Intravenous Ciprofloxacin Therapy in Respiratory Infections

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Abstract

Of the quinolone class of antimicrobials, only intravenous (IV) ciprofloxacin is currently available for treatment of various bacterial infections. Pathogens causing pneumonia in otherwise healthy adult patients may differ from those found in elderly patients, nursing home residents, alcoholics, and in individuals with debilitating diseases. Nosocomial pneumonias typically involve Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli. Aspiration pneumonia in the community most often involves anaerobes, but in the hospital S. aureus and Gram-negative organisms are commonly found. Based on these clinical and microbiological issues, a comparative evaluation of sequential IV and oral (PO) ciprofloxacin versus other antibiotics were reviewed and the results are summarized in this article. The focus is on the role of sequential intravenous/oral ciprofloxacin in the treatment of lower respiratory tract infection.

Key words: *Fluoroquinolones, ciprofloxacin, infection, respiratory tract, sequential therapy.*

The fluorinated quinolones represent a promising new class of antimicrobial agents with a broad range of activity against both Gram-negative and Gram-positive aerobic organisms. The first of the non-fluorinated quinolones, nalidixic acid, was developed in the 1960s. This agent was adequate for treatment of urinary tract infections caused by some Gram-negative organisms, but did not have sufficient tissue penetration after oral dosing to be of use in systemic infections. The rather rapid development of resistant bacteria and superinfection with resistant organisms, such as Pseudomonas aeruginosa, posed additional problems with its use.

The fluoroquinolones – norfloxacin, pefloxacin, enoxacin, ofloxacin, and ciprofloxacin – have excellent tissue penetration after oral administration. Tissue concentrations are well above the minimal inhibitory concentrations (MICs) for most Gram-negative and Gram-positive pathogens that may be encountered in clinical practice.

Ciprofloxacin is presently the only intravenous fluoroquinolone approved by the Food and Drug

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Table 1. Sensitivity of common respiratory tract pathogens to ciprofloxacin*

Sensitive	(MIC less than 1 mcg/m)
	Moraxella (Branhamella) catarrhalis
	Hemophilus influenzae
	Klebsiella sp.
	Neisseria sp.
	Pseudomonas aeruginosa
	Serratia marcescens
	Staphylococcus aureus
Intermediate	(MIC 1 to 2 mcg/mL)
	Mycobacterium tuberculosis
	Legionella sp.
	Streptococcus pneumoniae and other Streptococcus sp.
Resistant	(MIC greater than 4 mcg/mL)
	Anaerobic cocci
	Bacteroides sp.
	Pseudomonas maltophilia
	Pseudomonas cepacia
Insufficient data	Chlamydia sp.
	Mycoplasma sp.

*Inoculum size not a factor.

Administration for respiratory tract infection. It is active against many common pathogens of the respiratory tract, including Hemophilus influenzae, Streptococcus pneumoniae, Moraxella (Branhamella) catarrhalis, and P. aeruginosa. About 90% of Pseudomonas aeruginosa strains are inhibited by dose of less than 1 mcg/mL of ciprofloxacin. Some activity against Legionella and mycobacteria organisms has also been demonstrated. Ciprofloxacin has been shown to be effective against beta-lactamase-producing organisms and methicillin-resistant Staphylococcus aureus (both methicilin-susceptible, and to a lesser extent, methicillin-resistant strains).

The role of oral ciprofloxacin in the treatment of respiratory infections has been reviewed in a previous issue of this journal.[1] The oral formula is useful in managing acute bacterial exacerbations of chronic obstructive pulmonary disease and bacterial lower respiratory tract infections in diabetic, alcoholic patients and for treating elderly patients with respiratory tract infections, including nosocomial pneumonias.

This article reviews the current applications of sequential intravenous/oral ciprofloxacin in the treatment of lower respiratory tract infections. This review is based on the author's personal experience and a review of the current literature. The focus will be on the role of sequential IV/PO ciprofloxacin as monotherapy in serious lower respiratory tract infection, particularly nosocomial pneumonia with associated cost benefits.

Nosocomial pneumonia

According to the National Nosocomial Infections Surveillance (NNIS) System, nosocomial pneumonia is the second leading cause of hospital-acquired infections, accounting for approximately 13%-18% of all nosocomial infections in the United States. Hospital-acquired pneumonia occurs at a frequency of 0.6-1.0 episodes per 100 hospitalizaions and in 18% of postoperative patients. Intubated patients may have rates of pneumonia 7- to 12-fold higher than usual patients without a respiratory therapy device.[2]

Etiology of nosocomial pneumonia

Gram-negative bacilli are implicated in more than 60% of the reported cases of nosocomial pneumonia. Amongst these bacilli, Pseudomonas aeruginosa accounts for 17%, followed by Enterobacter spp (10%), Klebsiella pneumoniae (7%), Escherichia coli (6%), Haemophilus influenza (6%), Serratia marcescans (4.5%). Staphylococcus aureus comprises 14% of all nosocomial pneumonia pathogens with a particularly high prevalence in burn and surgical intensive care unit patients with wound infections. Streptococcus pneumoniae (3%), Haemophilus influenza and Branhamella catarrhalis are often present in elderly patients with chronic lung disease.[2]

Mortality, morbidity and cost of nosocomial pneumonia

Crude mortality rates for nosocomial pneumonia may range from 20% to 50% with an attributable mortality of 33%.[3]

Hospital-acquired pneumonia may prolong hospitalization by 8-9 days[3] and may increase the duration of mechanical ventilation or intensive care unit stay thereefold. Based on an estimated 40 million hospitalizations per year in the United States, the annual direct cost of diagnosing and treating nosocomial pneumonia exceeds $2 billion.[4]

Treatment of nosocomial pneumonia

Combination vs Monotherapy

In contrast to community-acquired pneumonias where monotherapy with antibiotics is often prescribed, based on the most likely causative organism, therapy of nosocomial pneumonia is often given as a combination of antibiotics. The combination used is for synergy and to adequately treat the wide range of organisms often found in nosocomial pneumonia, particularly in patients who have multiple comorbidity risk factors. Recommendations for treatment are: third-generation cephalosporin, or extended spectrum penicillins, or penicillinase-resistant penicillins, combined with one of the aminoglycosides like gentamicin, amikacin or tobramycin.[5] (Erythromycin must be added

Table 2. Monotherapy vs combination therapy for treatment of nosocomial pneumonia.

Monotherapy	Success rate percent	Combination therapy	Success rate percent
Cefoperazone[6]	87	Clindamycin & gentamicin, cefazolin & gentamicin	72
Aztreonam[7]	92	Tobramycin & clindamycin or vancomycin or Erythromycin or penicillinase-resistant penicillin	50
Ceftazidime[8]	88	Tobramycin & ticarcillin	83
Ceftazidime[9]	88	Tobramycin & cefazolin	92

whenever Legionella is suspected.) Over the past decade, a number of studies were done to evaluate the effectiveness of monotherapy against combination therapy for treatment of nosocomial pneumonias. Some of the results of these studies are tabulated in Table 2.

Subsequently, other studies using monotherapy with imipenem, aztreonam, third-generation cephalosporin (ceftazidime), ticarcillin/clavulanic acid were completed and showed overall success rates of 77%-96%.[10-14]

Other observations made from these studies showed that superinfection was higher with combination therapy (18% vs 12%), colonization rates were higher in patients receiving monotherapy (30% vs 20%), and persistence of Pseudomonas sp., Enterobacter sp. and Serratia sp. sometimes led to the development of resistance amongst these organisms. Thus, it appears that monotherapy as treatment of nosocomial pneumonia is effective, particularly with the use of the recently introduced potent cephalosporins, monobactams, and carbipenems.

Fluoroquinolones as monotherapy for nosocomial pneumonia

In view of the excellent in vitro susceptibility of the common nosocomial pneumonic pathogens – Pseudomonas aeruginosa, Enterobacter species, Klebsiella pneumonia, Escherichia coli, Haemophilus influenzae, Serratia marcescans, Staphylococcus aureus – against ciprofloxacin (Table 3), a number of studies were done in the United States and other countries to evaluate the safety and efficacy of sequential intravenous/oral (IV/PO) ciprofloxacin as a monotherapy in the treatment of nosocomial penumonia. The results of some of these clinical trials are summarized in the accompanying Table 4.

In reviewing the sixteen studies listed in Table 3 and 4, several features become obvious:

a. The sequential intravenous/oral ciprofloxacin achieves a high, acceptable success rate in the treatment of serious lower respiratory tract infections. The approved intravenous dose of ciprofloxacin is 400 mgm every 12 hours.

b. A common observation in most of the studies which merits special attention is the shorter duration of IV ciprofloxacin compared to the parenteral comparative drug. This, perhaps, results from the advantage which IV/PO ciprofloxacin offers regarding a predictable response since the spectrum of activity is the same for the IV and oral formulations. As a result, cost reduction can be a significant benefit of sequential therapy. These factors simplify the clinical decision to switch to an oral drug and represent an advantage of sequential ciprofloxacin therapy over traditional therapy with aminoglycosides or third-generation cephalosporins. For example, in one study,[22] the 56 ceftazidime-treated patients received, on an average, seven days of intravenous ceftazidime, followed by various currently available broad spectrum oral antibiotics for a variable period of time. The 66 cirprofloxacin-treate patients, on an average, received six days of intravenous ciprofloxacin, followed by an average of five days of oral ciprofloxacin, 500 mg twice daily. The daily cost of intravenous ceftazidime at Nassau County Medical Center is approximately $78/day, while oral 500 mgm twice/daily ciprofloxacin costs $4/day. Thus, in the ceftazidime group, 56 patients who received one extra day of intravenous ceftazidime, the extra cost was $4,144 (56 patients x 74).

c. From a pulmonologist's point of view, ciprofloxacin is very effective as monotherapy for Gram-negative infections of the lower respiratory tract. For staphylococcal infections, fluoroquinolones may also be effective. However, there are better drugs with a better spectrum of activity against anaerobes. Ciprofloxacin is quite effective for H. influenzae infection, as well M. catarrhalis, a common pathogen in respiratory infections. For S. pneumoniae infection, penicillin remains the drug of choice in healthy patients. However, in polymicrobial infections in which the pathogen is not identified prior to the start of therapy, ciprofloxacin is effective if S. pneumoniae is present. The sequential intravenous-to-oral ciprofloxacin regime is effective for serious LRTIs. It is possible to begin the IV formulation in a severely

Table 3. Comparative trials.

Investigator	Country	Study design	Comparative drug	No. pt.	Dosage	Clinical cure/ improvement	Duration of treatment I/V	Duration of treatment PO	%	Bact. brad. %	Commonest side effects with ciprofloxacin	Comments
Greene[19]	USA	Random double-blind	Ciprofloxacin	34	200 IV x 2 then 500-750 POx2	Equal in both groups.	6.6	NA	Equal in Both groups.		Increased hepatic enzymes, headache, increased theophylline levels.	Severe LRTI were included. Commonest isolate: Pseud. and H. influenza.
			Ceftazidime	37	1-2 gm IV x 2-3		9.2	NA				
Haddow[20]	USA		Ciprofloxacin	37	200 IV x 2 then then 750 POx2	36/37	6.6 + oral			62	Increased hepatic enzymes, nausea, increased theophylline levels in 3 patients.	Nosocomial pneumonia Pred. isolate, H. influenza, Pseudomonas aeruginosa.
			Ceftazidime	34	1-2 gm IV x 2-3	33/34	9.2	only		77		
Hirata-Dulas[21]	USA	Random	Ciprofloxacin	24	200-400 IV x 2 then 750 POx2	12/24	3.4 + 10.6		50	NA	Increased hepatic enzymes, eosinophils during treatment.	Comparable results in nursing home-acquired pneumonia. Cipro group received shorter parenteral therapy. Commonest pathogens: Strept. pneumonia, H. incluenza.
			Ceftriaxone	26	2 gm IV/24 hrs 1 gm IM/24 hrs	14/26	3.9 + 10.1		54	NA		
Khan F.[22]	USA	Random	Ciprofloxacin	66	200-300 IV x 2 then 500 POx2	60/66	6 + 5		91	90	Skin rash in 5/66, 3/66 developed superinfection.	Monotherapy with sequential IV/PO Cipro as effective as parenteral Ceftazidime. Significant cost savings in Cipro group (see text).
			Ceftazidime	56	1-2 gm IV x 2-3 then PO broad spectrum antibiotics.	50/66	7 + variable		87.5	90	Seizures (one), hallucinations (one), decrease WBC (one). 6/56 developed superinfection.	
Levine[23]	USA	Random double-blind	Ciprofloxacin	14	200 IV x 2	9/14	Total 8		71	70	Increase in 4 patients and decreased in one patient of platelet counts.	Severe LRTI-11 bacteremic and 18 nonbacteremic. Commonest isolate - Strep. pneumonia.
			Ceftazidime	15	2 gm IV x 3	12/15	Total 11.4		80	80		
Lode[24]	Germany	Random open	Ciprofloxacin	18	100 IV x 2-3 then 500 POx2	17/18	Total 16		94	NA	Nausea, rash, vomiting, arthralgia leading to discontinuation of therepy in three patients.	Serious LRTI. Commonest isolate-Pseud aeruginosa, E. coli, Staph. aureus.
			Imipenem/ Cilastin	24	500 IV x 4	19/24	Total 12		79			
Rapp[25]	USA	Randon double-blind	Ciprofloxacin	7	300 IV x 2	15/17	Total 11		88.2	30	Minimal eosinophilla and increased hepatic enzymes in 1 patient.	21/32 were ventilator dependent. Commonest isolates - E. coli, H. influenza, Kleb pneum, Proteus mirabilia.
			Ceftazidime	15	2 gm IV x 3	13/15	Total 11		86.7	53		
Trenholme[26]	USA	NA	Ciprofloxacin	23	200 IV x 2 then 500 x 2 oral	23/23	6.2 + 6.3			NA	Seizure in patient with history of underlying seizure disorders.	Nursing home and hospital acquired LRTI. Commonest organizm - coag. positive Staph, aureus, Kleb penum, Pseud aeruginosa, E. coli, Enterobacteriacea.
			Ceftazidime	21	2 gm IV x 3	15/21	6.9 + variable			NA		
Wintermantel[27]	NA	Random open	Ciprofloxacin	33	200 IV x 2 then 500 POx2	29/33	NA		88	NA	NA	NA
			Ticar/Clav	36	5,200 mgm x 3	32/36			89			

Dosage: All dosages in mgm unless noted otherwise.
NA: Not available
LRTI: Lower respiratory tract infection

Table 4. Non-comparative trials.

Investigator/ country	No. of pts.	Dosage	Clinical number	Core/ improvement %	Bact. brad. %	Duration IV/oral	Commonest side effects	Comments
Chrysanthopoulos/ Athens, Greece[28]	78	200 IV x 2 then 500 POx2	Not available (NA)	NA	NA	NA	Increased hepathic enzymes during treatment.	90 patients, (78 with LRTI, and 12 with biliary sepsis) were included with overall cure/improvement rate of 93.6%. Severe underlying diseases were present in most pts - COPD, CHF, diabetes, alcoholism, etc.
Giamerellout/ Athens, Greece[29]	15	200 IV x 2 only or followed by 750 POx2	15/15	100	60	15/10	Increased hepatic enzymes, increased BUN and creatinine with polyuric rental failure (patient was diabetic and dehydrated), nausea,	Difficult-to-treat infections with multiple-resistant organisms. Mechanical ventilation, ARDS, DM and cricitally ill patients.
Jacques and French multicenter study group/France[30]	13	200 IV x 2 then 750 POx2	10/13	76	70	11 and variable	Pain at site of IV, rash, headache and increased hepatic enzymes.	A total of 94 patients with serious bacterial infections were included. Clinical and bacterial cure was 92 and 73% resp.
Nix/New York, USA[31]	11	200 IX x 2	8/11	81.8	71.4	7-14 d		Nosocomial LRTI, elderly critically ill in the ICU.
Peloquin/New York, USA[32]	50	200-300 IV x 2	30/50	59	58	5-12 d	Pain at site of IV, fever, increased BUN and creatinine.	Gram-negative LRTI with multiple-resistant organisms only were included. Elderly ICU patients with malnutrition, vent-dependence and multiple underlying disease, 80% had received previous antimicrobial treatment.
Unertl/Germany[33]	10	200 IV x 2	8/10	80	80	NA	NA	Legionellosis in critically ill patients, including cases unresponsive to erythromycin and/or Rifampin.
Winter[34]/NA	10	200 IV x 4	6/10	60	60	NA	NA	All patients had Legionella pneumonia. In four patients, treatment was started late.

NA: Not available.

ill patient and, after a few days when the patient improves, switch to oral ciprofloxacin without the concern of changing dosages or that the new antimicrobial may not have the same spectrum of activity for the pathogens involved in the infection being treated.

d. Ciprofloxacin with its extended antimicrobial spectrum – antipseudomonal, antistaphylococcal, antienterobacteroceal – has proved to be a safe and effective therapeutic agent for nosocomial pneumonia caused by multiresistant organisms. The ability to switch to the oral form should allow ciprofloxacin to be a convenient and cost-effective alternative to current therapeutic regimes which require continued intravenous use with attendant risk of phlebitis and sepsis.

Areas of concern: emergence of resistance

Sporadic emergence of resistance occurs more often in Staphylococcus aureus and Pseudomonas aeruginosa – both with modest susceptibility against ciprofloxacin in the range of 0.5-2 ug/ml. Overall incidence among clinical isolates has been 2% and occurs with a frequency of $1 \times 10^{-8} - 1 \times 10^{-9}$ as[15] sequential multistep mutations leading to:

a) alteration of Topisomerase II of the bacterial DNA
b) decreased drug permeation.

The development of resistance may be related to the presence of barely inhibitory or subinhibitory concentration of the antibiotic preventing eradication and encouraging growth of clones of resistant strains.

Ciprofloxacin is effective against both methicillin-sensitive and methicillin-resistant Staphylococcus aureus (MRSA), coagulase-positive or coagulase-negative Staphylococcus aureus and promises to be an alternative to vancomycin for MRSA.[17] However, New York City hospitals showed an increase in the resistant strains of Staphylococcus aureus from 0.9% to 5.3% within a year after the introduction of ciprofloxacin to these hospitals.[17] Some authors are concerned that this resistance may spread from person to person,[18] particularly with MRSA.

In summary, it is clear that sequential intravenous/oral ciprofloxacin is very effective in the treatment of lower respiratory tract infection. Early institution of oral ciprofloxacin after a course of intravenous therapy is safe and can result in significant cost savings. With persistent pseudomonal and staphylococcal infections, the chances of emergence of drug resistance are present. To minimize this, it is extremely important to use this important new drug only in the proper settings, in adequate doses and not as an empiric treatment of respiratory infections, particularly those related to MRSA.

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