

Choosing the Ideal Antibiotic Therapy and the Role of the Newer Fluoroquinolones in Respiratory Tract Infections

An interview with Robert C. Owens, Jr., PharmD, Clinical Pharmacy Specialist, Department of Infectious Diseases, Maine Medical Center, Portland, Maine and Clinical Instructor, University of Vermont College of Medicine, Burlington, Vermont



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In addition to his position of Clinical Pharmacy Specialist in Infectious Diseases at the Maine Medical Center, Dr. Owens is a Clinical Instructor in the Department of Medicine at the University of Vermont College of Medicine in Burlington, Vermont. He has written a number of articles and book chapters on antimicrobial therapy, particularly relating to pharmacokinetics and pharmacodynamics. Dr. Owens has participated in numerous panel discussions and lectures at grand rounds and national and international meetings. He has served on the editorial board for *Antibiotics for Clinicians* for the past 3 years.

In this interview, Dr. Owens discusses the need to consider pharmacodynamic profiles of antibiotic agents and evaluates how 2 recently approved fluoroquinolones, gatifloxacin and moxifloxacin, for treatment of respiratory tract infections may offer a therapeutic advantage over other oral antimicrobials in patients at risk for resistant pneumococcal infection. He emphasizes that a collective awareness among both clinicians and patients regarding increasing antimicrobial resistance must exist to preserve these as well as other potent antibiotics.

Efficacy Considerations

AJMC: In general, what are the most important pharmacologic characteristics to consider when evaluating an anti-infective agent for efficacy?

Dr. Owens: Pharmacokinetics describes changes in tissue and serum concentrations of the drug over time, while pharmacodynamics relates these changes to a particular pharmacologic effect. In the case of antimicrobial agents, pharmacodynamic concepts describe a correlation between drug concentration and bactericidal activity over time.

Antimicrobial agents can be divided into 2 categories based on the patterns of bactericidal activity. For concentration-dependent bactericidal agents, such as the aminoglycosides and fluoroquinolones, the extent that the peak drug concentration exceeds the minimum inhibitory concentration (MIC) of the pathogen (or Peak:MIC ratio) and the area under the serum concentration versus time curve (AUC) to MIC ratio are the primary determinants of bactericidal activity. For gram-positive organisms, particularly *Streptococcus pneumoniae*, an AUC:MIC ratio of at least 30 has been associated with microbiologic eradication of the organism.

For the so-called time-dependent bactericidal antibiotics, such as the beta-lactams, macrolides, and clindamycin, the duration of drug expo-

sure rather than the magnitude of the drug concentration has been associated with optimal microbiologic and clinical outcomes.

It has become important to compare the pharmacodynamic profiles of agents within a class of antibiotics to choose those demonstrating superior pharmacodynamic profiles to optimize therapy in our patients and to delay or prevent the emergence of resistance.

Safety Considerations

AJMC: *What are the most important pharmacologic characteristics to consider when evaluating an anti-infective agent for safety?*

Dr. Owens: In terms of safety, the more important considerations involve the pharmacokinetic profile of the compound in question. The first of these is the route of metabolism and elimination. The second consideration is whether the agent interacts with the cytochrome P450 system. If the agent does interact, clinicians should consider which isoenzymes it induces, inhibits, or is a substrate of.

Because certain agents may accumulate in the presence of organ dysfunction and invoke drug-specific toxicities, the route of drug elimination—regardless of cytochrome P450 system interaction—is very important. Therefore, it is critical that studies be conducted in all patient types—those with varying hepatic function if the drug is hepatically metabolized, as well as those demonstrating varying renal function, including dialysis patients.

The elimination of active drug must also be considered, particularly in cases of antibiotics with anaerobic activity. Elimination of active antimicrobials via the gastrointestinal tract has been associated with the disruption of colonic flora as well as the development of vancomycin-resistant enterococci.

Drug Interactions

AJMC: *What is the clinical significance of drug interaction with the cytochrome P450 system?*

Dr. Owens: Many commonly utilized antibiotics undergo metabolism via the cytochrome P450 system, such as rifampin, ciprofloxacin, erythromycin, and clarithromycin, and there may be significant potential for drug-drug and drug-food interactions. With cytochrome P450 drug interactions, dramatic consequences, such as an increased risk of bleeding or embolic events, seizures, or fatal arrhythmias, may occur when patients on these antimicrobials are also concurrently receiving agents such as warfarin, phenytoin, theophylline, or certain antihistamines.

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Keep in mind that hepatic metabolism *not* involving the cytochrome P450 system must also be considered, as trovafloxacin toxicity has been associated with this pathway. It has also been suggested that a deficiency in conjugational enzymes may be responsible for toxic epidermal necrolysis, a severe and sometimes fatal dermatological consequence of drug exposure.

AJMC: *Are there any significant drug interactions with the fluoroquinolones?*

Dr. Owens: Certain fluoroquinolones (eg, sparfloxacin, grepafloxacin, and

moxifloxacin) have been associated with significant QT_c interval prolongation in patients. Prolongations in excess of 60 milliseconds from baseline or a total prolongation greater than 500 milliseconds pose a heightened risk of developing torsade de pointes, a potentially fatal ventricular arrhythmia. Combining 2 or more agents that prolong the QT_c interval should therefore be avoided because of the risk of additive QT_c prolongation and subsequent clinical sequelae. Because of recent concerns of fluoroquinolone toxicity, the FDA has recently placed a QT_c warning on all new quinolones, including the addition of a precautionary statement in the levofloxacin package insert.

In addition, oral fluoroquinolones should not be administered concurrently with polyvalent cationic compounds, such as sucralfate, magnesium- and aluminum-containing antacids, iron, and zinc, which lead to reduced absorption of the fluoroquinolone.

Unlike ciprofloxacin, which inhibits the metabolism of theophylline, the newer fluoroquinolones do not interfere with theophylline metabolism, as a result monitoring during therapy is not required.

Structural Characteristics Related to Adverse Events

AJMC: *Over the past few years, several fluoroquinolones have been associated with significant adverse events. Are there any specific structural characteristics or markers identified in these drugs that are related to these events?*

Dr. Owens: We recently presented data at the Infectious Diseases Society of America meeting in Philadelphia regarding specific fluoroquinolone toxicities that have an apparent structural relationship.¹ Of interest, the trifluorinated quinolones (trovafloxacin, temafloxacin, fleroxacin, and tosufloxacin) all have been associated with increased frequency

and severity of adverse events, and fatalities in some cases. Temafloxacin, trovafloxacin, and tosufloxacin all possess a 2,4 difluorophenyl group which, when attached to the quinolone or naphthyridone structure, appears to be associated with severe toxicity. Hemolytic uremic syndrome has been reported with temafloxacin, and severe hepatotoxicity with trovafloxacin. Sparfloxacin and lomefloxacin, as well as a number of compounds that have been withdrawn in development stages, such as clinafloxacin, have been associated with severe phototoxicity. An association has been made between phototoxicity and the placement of halides (chlorine or fluorine atoms) at the 8-position on the quinolone nucleus.

Now that these chemical configurations have been identified, it is unlikely we will see newer agents possessing such structural characteristics. Unfortunately, a relationship between QT_c prolongation potential and a specific structural refinement in compounds, such as grepafloxacin and moxifloxacin, has not been identified.

AJMC: *Two new fluoroquinolones were recently approved for respiratory tract infections. How do these agents compare with the older quinolones in terms of these structural relationships?*

Dr. Owens: These new agents, gatifloxacin and moxifloxacin, are termed 8-methoxy fluoroquinolones. Both compounds are monofluorinated and lack the structural proclivity to cause the severe toxicities associated with temafloxacin and trovafloxacin. Moreover, gatifloxacin's elimination pathways do not rely on the liver. In addition, unlike sparfloxacin, neither gatifloxacin nor moxifloxacin possess a halide at the 8-position that would predict significant phototoxic potential. This has been termed a significant advancement over previous compounds.

Certain quinolones have been associated with adverse effects involving the central nervous system (CNS) such as seizures. The substituted piperazinyl group at the 7-position of gatifloxacin results in a decreased affinity toward gamma-aminobutyric acid receptors within the CNS. In addition to these structural features, gatifloxacin is almost exclusively renally eliminated, with less than 1% of the administered dose undergoing hepatic metabolism.

Structure and Efficacy

AJMC: *Do the structural attributes of these newer agents offer potential efficacy advantages?*

Dr. Owens: The 8-methoxy group seen in both gatifloxacin and moxifloxacin has been determined to provide an enhanced affinity toward target binding sites in *S pneumoniae*. Specifically, these agents target both topoisomerase II (DNA gyrase) and topoisomerase IV. Most other fluoroquinolones preferentially bind to topoisomerase IV in pneumococci. Fluoroquinolones possessing the 8-methoxy group have been shown to select for resistance in isolates of *S pneumoniae* less frequently in vitro. However, whether these structural attributes will result in a delay in the emergence of resistant strains of *S pneumoniae* remains to be confirmed in clinical settings.

AJMC: *Overall, how do those fluoroquinolones compare with other agents (both fluoroquinolones and nonfluoroquinolones) in terms of efficacy?*

Dr. Owens: The pneumococcus has been increasing in resistance to agents such as the beta-lactams, sulfonamides, macrolides, and tetracycline derivatives. Fortunately, these newer fluoroquinolone agents have not followed this trend. For this reason, gatifloxacin and moxifloxacin

compare favorably to other commonly used antibiotics against the typical causes of respiratory tract infections, including resistant *S pneumoniae* and beta-lactamase-producing strains of *Haemophilus influenzae*. In addition, due to their activity against the atypical respiratory pathogens, the use of more expensive beta-lactam/macrolide combination regimens can be minimized and replaced with once-daily monotherapeutic alternatives.

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Microbiological Profile

AJMC: *Could you describe the microbiological profiles of these new agents?*

Dr. Owens: The microbiologic activity of gatifloxacin and moxifloxacin compares similarly to levofloxacin, with the exception of their having a greater potency against *S pneumoniae*. Gatifloxacin and moxifloxacin remain active against penicillin-susceptible pneumococci as well as penicillin-nonsusceptible strains and are active against staphylococci that remain methicillin-sensitive and against *H influenzae* and *Moraxella catarrhalis*, including beta-lactamase-positive strains of each.

Because of their good intracellular penetration and excellent in vitro activity against the atypical respiratory tract pathogens (eg, *Chlamydia pneumoniae*, *Mycoplasma pneumo-*

niae, and *Legionella pneumophila*), both agents are excellent choices for the treatment of infection caused by these organisms. Both offer additional antianaerobic activity over levofloxacin, which may be beneficial in respiratory tract infections involving upper airway anaerobes.

Pharmacology

AJMC: *What are the pharmacological characteristics of these agents?*

Dr. Owens: Both gatifloxacin and moxifloxacin have a relatively long half-life, which supports their once-daily dosing schedules. Achievable AUC:MIC ratios with both agents far exceed 30, the commonly used pharmacodynamic breakpoint for *S pneumoniae*; and for common members of the enterobacteriaceae family, their AUC:MIC ratios exceed 125. The pharmacodynamic profiles of gatifloxacin and moxifloxacin predict their efficacy against the commonly associated respiratory tract pathogens. In addition, the possession of an 8-methoxy group may select for resistant isolates during therapy less frequently.

Moxifloxacin is almost completely absorbed following oral administration, which is characteristic among most fluoroquinolones. Following oral absorption, nearly 25% of active drug is excreted through the GI tract. Moxifloxacin is metabolized significantly by the liver, but it lacks interaction with the cytochrome P450 enzyme system.

Because of its once-daily dosing schedule, availability in both intravenous and oral dosing forms, excellent oral bioavailability, and good tolerability profile, gatifloxacin is certainly a valuable agent in transitional therapy programs. Moxifloxacin is not available in an intravenous formulation, which currently will hinder its usage within institutional settings. However, an intravenous formulation of moxifloxacin is under development.

Cardiac Toxicity

AJMC: *Are there any concerns regarding cardiotoxicity with these newer fluoroquinolones?*

Dr. Owens: As far as potential for QT_c prolongation is concerned, the use of gatifloxacin is cautioned in patients at risk for cardiac toxicity due to QT_c prolongation, such as those receiving class I and III antiarrhythmics or those with hypokalemia or bradycardia. Clinical trials conducted with gatifloxacin did not exclude patients taking these agents or with these medical conditions, and no QT_c-associated adverse cardiac events were described. In addition, QT_c prolongation greater than 60 milliseconds from baseline did not occur during administration of gatifloxacin nor was a total QT_c interval greater than 500 milliseconds noted. Additional studies in these populations are currently being conducted.

Moxifloxacin has been associated with QT_c prolongation similar to other marketed antibiotics, such as grepafloxacin, sparfloxacin, and erythromycin. The overall incidence of cardiac-related adverse events will be ascertainable over a period of time and use.

Current Management Strategies

AJMC: *Where do you see these 2 agents fitting in current management strategies for treating community-acquired respiratory tract infections?*

Dr. Owens: Both gatifloxacin and moxifloxacin have demonstrated clinical efficacy in the treatment of respiratory tract infections. The choice of which newer quinolone to use will probably be based on individual safety, tolerability profiles, and cost. However, the appropriate use of these compounds, as well as other antimicrobial agents, should be strongly emphasized. In patients who are otherwise healthy and probably not at risk for infection caused by a resistant

pneumococcal strain, agents other than these newer fluoroquinolones should be employed when possible. In patients at risk for resistant pneumococcal infection, such as those receiving previous courses of antimicrobial therapy, those having comorbid disease or receiving corticosteroids, and those having exposure to day care populations, to name a few, the newer generation fluoroquinolones may offer a therapeutic advantage.

...REFERENCE ...

1. Owens RC Jr, Ambrose PG, Wikler M. Review of structure-toxicity relationships of fluoroquinolones. Presented at the Infectious Diseases Society of America, 37th Annual Meeting, Philadelphia, PA, November 18-21, 1999. Abstract No. 94.