Ciprofloxacin*

Class: Fluoroquinolone

Overview

Ciprofloxacin is a second generation fluoroquinolone carboxylic acid derivative that exhibits primarily Gram-negative activity. Ciprofloxacin is the most active fluoroquinolone against *P. aeruginosa.* This drug is administered orally and parenterally. Forms of ciprofloxacin are available for intravenous (IV), intramuscular (IM) and subcutaneous (SC) administration. The drug is not labeled for veterinary use. Ciprofloxacin bioavailability fluctuates in dogs and can be as low as 40%. In ruminants, due to the function and structure of the stomachs, bioavailability can be as low as 20%. Ciprofloxacin is partially metabolized and a proportion is excreted in unchanged form. Ciprofloxacin is excreted both in the urine and in the bile. Side effects from the use of ciprofloxacin are fairly frequent, but most are mild and reversible and are frequently associated with prolonged usage.

Resistance

Low-frequency chromosomal mutational resistance to fluoroquinolones accomplished through modification of the DNA gyrase enzyme has been identified as the primary mode of resistance. An active efflux pump that limits the intracellular accumulation of the antimicrobial is an additional mechanism of resistance. This "efflux pump" resistance has been identified in several bacterial genera, including *Escherichia, Klebsiella, Staphylococcus, Streptococcus* and *Bacteroides* species. Cross resistance does occur between closely related quinolones. Neither of these mechanisms of resistance explain the recent ease of development of resistance in previously susceptible organisms or the associated resistance to other agents. Plasmid mediated resistance, once thought to be rare, conferred through the Qnr protein and AAC(6')-Ib-cr, a variant aminoglycoside acetyltransferase, are two mechanisms that appear to be becoming more and more prevalent. The Qnr protein protects the DNA gyrase, thus protecting target organisms from destruction due to lethal breaks in DNA. The variant aminoglycoside acetyltransferase reduces ciprofloxacin activity to a point of causing low level resistance. All of these means of resistance occur individually at relatively low levels, but the combination of these resistance mechanisms is precipitating severe reductions in drug efficacy. Cotransmission of these genes with extended spectrum β-lactamases (ESBLs) and carbapenemases are accelerating the many problems with antimicrobial resistance.

Resistance to ciprofloxacin is thought to be a growing problem worldwide and is evidenced by increases in ciprofloxacin resistance in ESBL producing *E coli* and *Klebsiella pneumoniae* in both hospital and community acquired bacteremias. Increased resistance is also being observed in *Enterobacter* and *Acinetobacter* species and to enterobacteriaciae in general. Ciprofloxacin sensitivity exhibited by Gram-negative organisms can be inferior to other antimicrobials, such as gentamicin, amikacin, imipenem and piperacillin-tazobactam, when multi drug resistant organisms featuring

ESBLs are present. A study from the United Kingdom in 2002 indicated that about 10% of isolates of *Neisseria gonorrhoeae* were resistant to ciprofloxacin. Resistance of Gram-positive organisms to ciprofloxacin has also been demonstrated. Most strains of community acquired methicillin resistant *Staphylococcus aureus* (MRSA) remain susceptible to fluoroquinolones, while hospital acquired strains are generally resistant. In a study of patients at the F.I Proctor Institute in San Francisco, CA from 1998 to 2006, it was found that the majority of MRSA ocular infections were resistant to ciprofloxacin. Although not exhibiting as broad a spectrum as newer quinolones like gatifloxicin, ciprofloxacin is generally effective against ocular infections, with the exception of MRSA and coagulase negative staphylococci.

Cross resistance among ciprofloxacin and other fluoroquinolones occurs. Evidence exists that use of fluoroquinolones in food animals is associated with increasing resistance against antimicrobials like ciprofloxacin. An association of molecular subtypes of isolates from poultry and of those from Minnesota residents suggests that resistant infections may be acquired through consumption of food. In a case control study conducted at Centers for Disease Control and Prevention's (CDC's) Foodborne Diseases Active Surveillance Network (FoodNet) sites in 1998 and 1999, persons with ciprofloxacin resistant *Campylobacter* were more likely to have consumed cooked poultry in commercial establishments then controls who were not ill. The National Antimicrobial Resistance Monitoring System (NARMS) reported that from 1997 to 2001, the percentage of ciprofloxacin resistant *Campylobacter jejuni* and *Campylobacter coli* infections increased from 13% (28/217) to 19% (75/384). This increase is statistically significant (odds ratio: 2.4, 95% confidence interval: 1.4-4.1). It is interesting to note that sarafloxacin was approved for use in food animals in 1995 and enrofloxacin was approved for use in food animals in 1996. The Food and Drug Administration estimates that the use of fluoroquinolones in poultry is responsible for compromising the therapy of nearly 10,000 people each year, through increased resistance to fluoroquinolones.

Fluoroquinolones are the antimicrobials most commonly utilized against invasive adult *Salmonella* infections and emergence of fluoroquinolone resistant *Salmonella* is also a concern. From 1996 to 2001 NARMS observed the decreased susceptibility of *Salmonella* isolates to ciprofloxacin. In many of these isolates only a single point mutation is required for decreased susceptibility, increased minimum inhibitory concentration, to become complete resistance. However, the preponderance of resistance to *Salmonella* isolates is linked to foreign travel and the subsequent introduction of resistant microbes to domestic healthcare facilities. Therefore the emergence of fluoroquinolone resistance to *Salmonella* may be associated with nosocomial infections and not with agricultural antimicrobial use.

Effectiveness

Ciprofloxacin is used in the treatment of respiratory, ocular (superficial and deep), intestinal, urinary, skin, prostate, bone, joint, meningeal, encephalitic and systemic infections. The drug is commonly used in the treatment of deep-seated infections and in the treatment of intracellular pathogens. In addition, ciprofloxacin is used for its effectiveness against *P. aeruginosa,* aerobic Gram-negative bacilli (especially as oral

therapy in hospital acquired pneumonias) and vancomycin susceptible enterococci. Oral ciprofloxacin, due to bioavailability, pharmacokinetic properties and reduced cost in comparison with injectable antimicrobials, is considered a viable option for pre-surgical antimicrobial prophylaxis in several surgical procedures. Due to increased resistance to fluoroquinolones in *Campylobacter* isolates, erythromycin, not ciprofloxacin, is once again considered the drug of choice in treating *Campylobacter* infections.

***References available by request. Call the Infectious Disease Epidemiology Section, Office of Public Health, Louisiana Department of Health and Hospitals (504-219-4563)**