CLINICAL USE OF AMINOGLYCOSIDES AND FLUOROQUINOLONES

Douglas Black, Pharm.D.
Associate Professor
School of Pharmacy
University of Washington
dblack@u.washington.edu

THE AMINOGLYCOSIDES: 1944-1975

Drug	Year	Source organism
Streptomycin	1944	*Streptomyces griseus*
Neomycin	1949	*Streptomyces fradiae*
Kanamycin	1957	*Streptomyces kanamyceticus*
Paromomycin	1959	*Streptomyces rimosus*
Spectinomycin	1962	*Streptomyces spectabilis*
Gentamicin	1963	*Micromonospora purpurea*
Tobramycin	1968	*Streptomyces tenebrarius*
Sisomicin	1972	*Micromonospora inyoensis*
Amikacin	1972	Semisynth deriv of kanamycin
Netilmicin	1975	Semisynth deriv of sisomicin

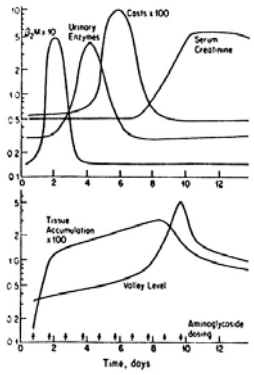
THE AMINOGLYCOSIDES: QUICK SUMMARY

- Generally used only when necessary (less toxic drugs are preferred)
- IV/IM, occasionally intrathecal; PO for certain GI infections
- Bactericidal
- Usually combined with a β-lactam for serious Gram-negative infections including *Pseudomonas*
- Also used (in lower doses) to help drugs for Gram-positive infections work better
- Occasionally used for mycobacterial infections
- Resistance is a significant issue
- TOXIC!!!
  - nephrotoxic (probably due to drug accumulating abnormally in the renal cortex)
  - ototoxic
    - auditory (starting at high frequencies)
    - vestibular (can be extremely debilitating)
  - enhancement of neuromuscular blockade (rare)

WHICH IS WORSE: NEPHROTOXICITY OR OTOTOXICITY?

KIDNEY	EAR
Reversible	Irreversible
Well-defined risk factors*	Poorly-defined risk factors
Well-defined time course (see next slide)	Poorly-defined time course
Monitor serum creatinine	No simple lab values to monitor
Serum concentrations correlate	Poor correlation with serum concentrations

*advanced age, duration of therapy, hypotension, concomitant liver disease, use of other nephrotoxins



AMINOGLYCOSIDE DOSING CHART

1. Select Loading Dose in mg/kg [IDEAL WEIGHT] to provide peak serum levels in range listed below for desired aminoglycoside.

AMINOGLYCOSIDE	USUAL LOADING DOSES	EXPECTED PEAK SERUM LEVELS
Tobramycin Gentamicin	1.5 to 2.0 mg/kg	4 to 10 μg/ml
Amikacin Kanamycin	5.0 to 7.5 mg/kg	15 to 30 μg/ml

2. Select Maintenance Dose (as percentage of chosen loading dose) to continue peak serum levels indicated above according to desired dosing interval and the patient's corrected creatinine clearance.*

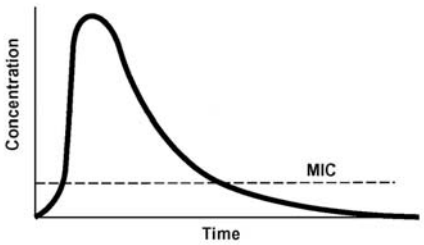
PERCENTAGE OF LOADING DOSE REQUIRED FOR DOSAGE INTERVAL SELECTED				
Ccr (ml/min)	half life† (hrs)	8 hrs	12 hrs	24 hrs
90	3.1	84%		
80	3.4	80		
70	3.9	76		
60	4.5	71		
50	5.3		79	
40	6.3		72	
30	8.4		63	
25	9.9		57	
20	11.9		50	
17	13.6			70
15	15.1			67
12	17.9			61
10‡	20.4			56
7	25.9			47
5	31.5			41
2	46.8			30
0	69.3			21

MEASUREMENT OF GENTAMICIN AND TOBRAMYCIN SERUM CONCENTRATIONS

Infection	Peak conc (μg/ml)	Trough conc (μg/ml)
Gram-positive	3	< 1
Gram-negative (except pneumonia)	5-8	< 1
Gram-negative pneumonia	10-12	< 1

CRITICAL: the peak is measured one hour after an infusion begins; the trough is measured immediately prior to the next dose (all done at steady state)

"EXTENDED-INTERVAL" AMINOGLYCOSIDE THERAPY



AMINOGLYCOSIDE THERAPY THAT WENT TERRIBLY WRONG

- 67 yo male, retired, very active. Chief complaint: 3 month history of dizziness
- Treatment: mitral valve replacement, 4-week course of nafcillin/gentamicin
- Patient stayed in the hospital for a week, discharged on home IV antibiotics
- Immediately complained of dizziness to the home care nurse and consulting pharmacist

FLUOROQUINOLONES BY GENERATION

FIRST[1]	SECOND[2]	THIRD[3]	FOURTH[4]
All obsolete	Ciprofloxacin	Moxifloxacin	-
-	Levofloxacin	Gemifloxacin	-

[1]nalidixic acid, cinoxacin, oxolinic acid

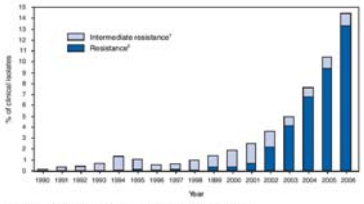
[2]obsolete: norfloxacin, enoxacin, lomefloxacin, ofloxacin

[3]gatifloxacin (Tequin) withdrawn from the market in 2006

[4]trovafloxacin (Trovan) withdrawn from the market because of hepatotoxicity

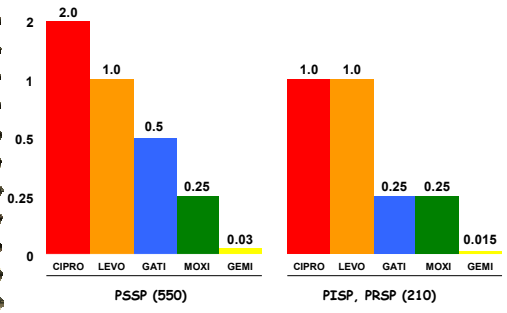
MMWR 2007; 56(14): 325-360 (April 13, 2007)
http://www.cdc.gov/mmwr

FIGURE. Percentage of *Neisseria gonorrhoeae* isolates with intermediate resistance or resistance to ciprofloxacin, by year — Gonococcal Isolate Surveillance Project, United States, 1990–2006*

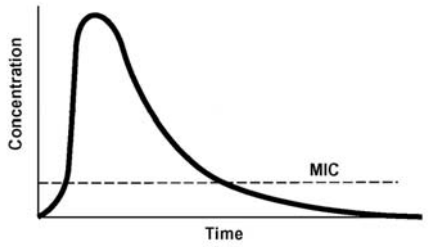


*Data for 2006 are preliminary (January–June only).
†Demonstrating ciprofloxacin minimum inhibitory concentrations (MICs) of 0.125–0.500 μg/mL.
§Demonstrating ciprofloxacin MICs of ≥1.0 μg/mL.

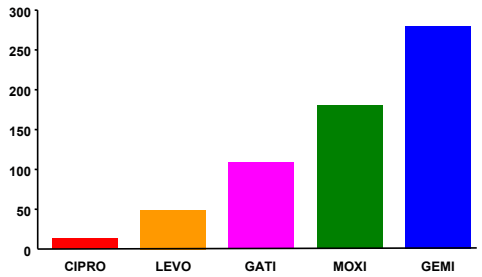
FLUOROQUINOLONE ACTIVITY AGAINST *STREPTOCOCCUS PNEUMONIAE* (MIC_{90} in mcg/ml)



AUC/MIC: THE BEST WAY TO DESCRIBE FQ ACTIVITY



AUC/MIC RATIOS FOR *S. PNEUMONIAE*



TOXICITY ASSOCIATED WITH FLUOROQUINOLONES

GI: nausea, vomiting, diarrhea, abdominal pain

CNS: HA, dizziness, sleep disturbance, confusion, seizure

Liver: increased LFTs, hepatitis, liver failure

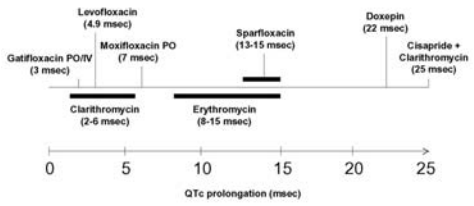
Kidney: hematuria, crystalluria, nephritis, renal failure

Musculoskeletal: tendinitis, arthropathy, tendon rupture

Cardiovascular: hypotension, tachycardia with QTc changes

Skin: rash, pruritis, photosensitivity

Endocrine: disturbance in glucose homeostasis



FLUOROQUINOLONES: THE BOTTOM LINE

1. These are HEAVILY used drugs (usually PO, sometimes IV). There is great fear that overuse will lead to the demise of the entire class. Some evidence for this already exists.
2. FQs are popular because they are bactericidal against many important pathogens, and they are very well tolerated.
3. Levofloxacin is the workhorse. It is the drug of choice in a growing number of UTI patients. It is commonly used for community-acquired pneumonia and sinusitis. It has other uses as well, such as traveler's diarrhea and STDs.
4. Ciprofloxacin is similar to levofloxacin except that it is less potent for Gram-positives, and its half-life is shorter. Moxifloxacin is theoretically the best FQ for Gram-positive organisms.
5. The most common side effect is GI. Photosensitivity can be a problem. FQs rarely have caused tendon rupture. They are probably not toxic to developing cartilage in humans.
6. Only ciprofloxacin precipitates metabolic drug interactions. The absorption of all FQs is affected by metal ions, however (e.g. aluminum, magnesium).