Aminoglycosides

I. HISTORY AND STRUCTURAL CHARACTERISTICS

Streptomycin was first isolated from *Streptomycyes griseus* by Waksman and colleagues in 1943. Kanamycin isolated in 1957 – drug of choice until 1963. Gentamicins first isolated from a micromonospora species. Tobramycin & netilmicin developed later as alternatives to gentamicin. Amikacin, a semisynthetic analog, is used for infections resistant to the other aminoglycosides (AGs). All AGs contain 2 or more aminosugars linked by glycosidic bonds to an aminocyclitol ring. In streptomycin, the aminocyclitol ring is streptidine, whereas in the other agents this moiety is 2-deoxystreptamine.

II. MECHANISM OF ACTION

AGs bind irreversibly to the 30S ribosomal subunit to decrease initiation and thus inhibit protein synthesis. However, AGs are bactericidal, whereas most protein synthesis inhibitors are bacteriostatic.

III. SPECTRUM

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acinetobacter calcoaceticus</th>
<th>Citrobacter freundii</th>
<th>Enterobacter cloacae</th>
<th>E. coli</th>
<th>Klebsiella pneumoniae</th>
<th>Other Proteus</th>
<th>Proteus mirabilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>%S  #</td>
<td>%S  #</td>
<td>%S  #</td>
<td>%S  #</td>
<td>%S  #</td>
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<tr>
<td>Ampicillin</td>
<td>0  25</td>
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<td>67  1866</td>
<td>0  376</td>
<td>0  31</td>
<td>95  194</td>
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<td>Ampicillin/ Sulbactam</td>
<td>89  62</td>
<td>0  62</td>
<td>78  67</td>
<td>67  91</td>
<td></td>
<td></td>
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<tr>
<td>Cefazolin</td>
<td>0  0</td>
<td>0  0</td>
<td>93  90</td>
<td>0  96</td>
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<tr>
<td>Cefazidime*</td>
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<td>100  88</td>
<td>100  100</td>
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<td></td>
<td></td>
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<td>Cefotetan</td>
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<td>97  97</td>
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<td></td>
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<td>Chloramphen. --</td>
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<td>NT</td>
<td>NT</td>
<td>NT</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>84  95</td>
<td>96  98</td>
<td>99  100</td>
<td>100  96</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>Piperacillin</td>
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<td>90  96</td>
<td>99  99</td>
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<td>Tetracycline†</td>
<td>64  84</td>
<td>78  81</td>
<td>80  26</td>
<td>0  0</td>
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<td></td>
</tr>
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<td>Tobramycin</td>
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<td>99  99</td>
<td>100  96</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TMP-SMX</td>
<td>89  84</td>
<td>82  88</td>
<td>95  94</td>
<td>90  95</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*non-urine isolates only †urine isolates only

Data from Regions Hospital, St. Paul, 1999.
Structures of the Aminoglycoside Antibiotics

Gentamicin

$C_1 \ R_1 = R_2 = CH_3$
$C_{1a} R_1 = R_2 = H$
$C_2 \ R_1 = CH_3, R_2 = H$

Tobramycin

Netilmicin

Amikacin

Streptomycin
Aminoglycosides have a broad spectrum that includes aerobic and facultative gram-negative bacilli and Staph. aureus. Susceptibility data is shown on the previous page. Streptococci, Pseudomonas cepacia, and Xanthomonas (Pseudomonas) maltophilia are generally resistant. Amikacin should be held in reserve and used only for resistant infections. Susceptibility and average MIC values will vary from institution to institution. Most large hospitals will compile these data in order to study trends of resistance. The data shown on the previous page were compiled at the Saint Paul Ramsey Medical Center in 1999.

IV. USES

a.) Serious gram negative infections due to Pseudomonas aeruginosa, E. coli, Enterobacter, Klebsiella, Proteus mirabilis, indole positive Proteus, Morganella morganii, Providencia retgerri and stuartii, and Serratia.

b.) Enterococcus endocarditis (combined with ampicillin or Pen G or vancomycin)

c.) Mycobacterium tuberculosis - amikacin and streptomycin may be useful for resistant strains. They may also be useful for Mycobacterium avium complex in AIDS.

d.) Staphylococcal infections (second line agent when β-lactams are contraindicated)

e.) Mixed aerobic-anaerobic infections. Gentamicin + clindamycin is good combination for pelvic inflammatory disease.

f.) Neisseria gonorrhoeae - Spectinomycin (single 2g IM dose) is alternative in patients who are allergic to ceftriaxone or in treatment failures.

V. RESISTANCE

Since AGs are generally reserved for serious infections that may be life-threatening, resistance to these agents may result in the death of the patient. Thus it is critical that resistance patterns be understood and that the mechanisms of resistance be identified. High level resistance to enterococci is increasing in most hospitals. There are three major mechanisms of resistance:

a.) Resistance due to production of plasmid-mediated AG modifying enzymes. This mechanism is most common and involves conjugation of the AG with either an acetyl group, an adenyl group, or a phosphoryl group. Plasmids can infect other gram-neg. bacteria - may lead to multiple resistance mechanisms especially in institutional settings.
• Kanamycin and Neomycin inactivated by phosphorylation at the 3' position. The newer AGs lack a 3'OH group and thus are resistant to this inactivating enzyme.
• Tobramycin, Gentamicin, and Netilmicin may be inactivated by 2''-adenylation and acetylation at the 2', 6', and 3 positions.
• Amikacin is inactivated by 6'-acetylation and is resistant to the other inactivating enzymes. Consequently, amikacin may be useful for bacterial infections that are resistant to the other AGs and should be held in reserve.

b.) Resistance due to ineffective transport into bacteria or active efflux out of bacteria.

c.) Ribosomal resistance - generally requires multiple mutational events because more than one ribosomal binding site is present for the deoxystreptamine aminoglycosides. High level clinical resistance by this mechanism is rare.

VI. DISPOSITION, METABOLISM, AND EXCRETION

a.) AGs are polar bases that exhibit poor oral bioavailability, low protein binding, and are excreted unchanged almost exclusively by glomerular filtration. These compounds do not cross the blood brain barrier well, even when the meninges are inflamed.

TABLE 37. PHARMACOKINETIC PARAMETERS OF AMINOGLYCOSIDES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Bio-Availability</th>
<th>% Protein Binding</th>
<th>Adult Half-life</th>
<th>Therapeutic Range (Peak)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
<td>Anephric</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Negligible</td>
<td>&lt;10%</td>
<td>0.8-2.8 h</td>
<td>28-87 h</td>
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<tr>
<td>Gentamicin</td>
<td>Negligible</td>
<td>0-30%</td>
<td>2.0-2.5 h</td>
<td>21-70 h</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>Negligible</td>
<td>0-30%</td>
<td>2.0-2.5 h</td>
<td>32-52 h</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Negligible</td>
<td>0-30%</td>
<td>2.0-2.5 h</td>
<td>27-70 h</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Negligible</td>
<td>0-30%</td>
<td>2.0-2.5 h</td>
<td>100 h</td>
</tr>
</tbody>
</table>

As the clearance of AGs is dependent upon glomerular filtration, one can adjust doses based on the creatinine clearance or serum creatinine in an individual patient. Due to the high incidence of serious adverse effects, it is important to monitor levels in plasma to ensure that adequate concentrations are achieved and to prevent toxicity. Generally, immunoassays are employed in most hospitals for AG determinations either by EMIT, FPIA, SLFIA, or RIA procedures. At many hospitals, a pharmacokinetics service run by a clinical pharmacist will be responsible for calculating doses.
Dosing of AGs may be done empirically e.g. 80 mg every 8 hours, but more commonly a predictive method based on body weight and adjusted for renal function based on serum creatinine is used. Initial parameter estimates may be determined by use of formulas that include lean body weight and serum creatinine as shown below:

**Determination of Lean Body Weight (LBW)**

LBW (male)  =  $50 + 2.3 \times (# \text{ of inches greater than 5'0''}) \text{ kg}$

LBW (female)  =  $45 + 2.3 \times (# \text{ of inches greater than 5'0''}) \text{ kg}$

**Determination of Creatinine clearance (CrCl)**

For males:  

\[
\text{CrCl} = \frac{(140-\text{Age}) \times \text{LBW}}{72 \times (\text{serum creatinine})}
\]

For females:  

\[
\text{CrCl} = 0.85 \times (\text{CrCl male})
\]

**Elimination rate constant of the aminoglycoside ($k_e$)**

\[
k_e = 0.0024 \times (\text{CrCl}) + 0.01 \text{ hr}^{-1}
\]

**Volume of distribution (V)**

\[
V = 0.15 - 0.30 \times (\text{LBW})
\]

\[
\frac{0.693}{k_e}
\]

Appropriate duration of sampling should be $>1.5 \times t_{1/2}$

Various nomograms have been developed for initial predictions, however the maximum variation in AG elimination has been estimated to be between 25-50%\(^1\\). Consequently an individualized pharmacokinetic approach such as the Sawchuk-Zaske method\(^2\\) will provide superior results. Currently, AG dosing and monitoring is quite controversial. Some infectious disease specialists are recommending single daily dose therapy such that the ratio of the highest serum concentration to the MIC\(_{90}\) of the bacteria is at least 10:1. In animal models, this approach appears to maintain efficacy and reduce toxicity and appears to be well tolerated in patients.


VII. ADVERSE REACTIONS

a.) Nephrotoxicity - characterized by decrease in glomerular filtration rate - almost always reversible. Toxicity may be increased by co-administration with vancomycin.

Neomycin > Gentamicin = Amikacin = Netilmicin >Tobramycin >Streptomycin

b.) Ototoxicity - may be either loss of hearing esp. high tone frequency or loss of vestibular function (tinnitus, vertigo). Usually irreversible.

Streptomycin = Kanamycin > Amikacin = Gentamicin = Tobramycin > Netilmicin

c.) Neuromuscular blockade - rare, but serious - usually a result of rapid iv administration or peritoneal irrigation. Treat by prompt administration of calcium.

d.) Hypomagnesemia - may occur in up to 1/3 of patients with restricted oral diet

e.) Contact dermatitis - especially with neomycin

VIII. INTRAVENOUS PRODUCTS

Amikacin - Amikin® (Apothecon) - 50 mg/ml and 250 mg/ml injection
Gentamicin sulfate - Garamycin® (Schering) - 2, 10, and 40 mg/ml injection
Kanamycin - Kantrex® (Apothecon) - 75 mg, 500 mg, and 1 g injection
Netilmicin sulfate - Netromycin® (Schering) - 100 mg/ml injection
Streptomycin sulfate - 400mg/ml
Tobramycin sulfate - Nebcin® (Lilly) - 10 mg/ml and 40 mg/ml injection. 30 mg/ml powder for injection

Admixture incompatibility: when β-lactams are mixed with AGs. Penicillins and cephalosporins inactivate AGs (ticarcillin and carbenicillin are worst). Tobramycin and gentamicin are more susceptible than netilmicin or amikacin. Incompatibility will occur when agents are mixed in same container or during the AG assay procedure.

Ticarcillin and carbenicillin may decrease aminoglycoside levels, especially in patients with poor renal function.

Sample handling - if patients are on concurrent β-lactam therapy

1.) Place sample on ice immediately after drawing and test sample immediately

2.) If assay is delayed, freeze sample. However inactivation can still occur when the specimen is frozen. If samples are to be frozen for long periods, inactivate penicillin with penicillinase.

3.) Draw aminoglycoside level when β-lactam is at trough level
IX. TOPICAL PRODUCTS

Aminoglycosides for Inhalation

Tobramycin - TOBI® (PathoGenesis Corp)

*Treatment of Pseudomonas aeruginosa infections in cystic fibrosis patients*

5 ml ampules containing 300 mg tobramycin administered with a PariLC Plus reusable nebulizer and a DeVilbilss Pulmo-Aide compressor.

Dose: 300 mg twice daily for 28 days.

Ophthalmic Ointments and Solutions

Tobramycin - Tobrex® (Alcon) - Ointment - 3 mg/g, Solution 3 mg/ml

Bacitracin Zinc-Neomycin-Polymyxin B Ointment - Neosporin® Ophthalmic Ointment (GSK)

Neomycin-Polymyxin B-Gramicidin Solution - Neosporin® Ophthalmic Solution (GSK)

Neomycin - 1% Hydrocortisone Suspension - Cortisporin® (GSK), Neo-Cortef (Upjohn)

Bacitracin Zinc-Neomycin-Polymyxin B Ointment + 1% Hydrocortisone - Cortisporin® (GSK)

Topical Creams and Ointments (selected from the many available)

Usually these are sold as combination products to widen the antibacterial spectrum.

Bacitracin Zinc-Neomycin-Polymyxin B Ointment - Neosporin® (Glaxo-SK), Mycitracin®

Triple Antibiotic Ointment (Upjohn), Mycitracin Plus Ointment & Campho-Phenique®

Antibiotic Plus (Winthrop) (the latter two also contain 40 mg lidocaine/g).

Neomycin sulfate cream - Myciguent® (Upjohn)

Genitourinary Irrigant - used to prevent infections in patients with indwelling catheters

Neomycin sulfate (40 mg/ml) + Polymyxin B (200,000 units/ml) - Neosporin® G.U. (GSK)

Oral aminoglycosides - used for gut sterilization prior to intestinal and colon surgery and to treat hepatic coma (NH₃-producing bacteria). Paromomycin is used to treat intestinal amebiasis and other parasitic infections. Oral neomycin has been shown to lower LDL cholesterol by 24%.

Kanamycin Sulfate - Kantrex® (Apothecon) - 500 mg capsules

Neomycin Sulfate Tablets -500 mg, Neomycin Oral Solution - Mycifradin® (Pharmacia Upjohn)

Paromomycin Sulfate - Humatin® (Parke-Davis) 250 mg capsules
Tetracyclines

I. HISTORY AND MECHANISM OF ACTION

The first tetracycline, chlortetracycline, was isolated from the soil organism Streptomyces aureus in 1949 by Duggar. Tetracycline was first produced by catalytic hydrogenation in 1953. The long-acting tetracyclines doxycycline and minocycline were introduced in the mid 1960's. Tetracyclines enter bacteria by an energy-dependent process and then bind to the 30S ribosomal subunit reversibly blocking the binding of aminoacyl-tRNA to the acceptor site on the mRNA-ribosomal complex. The net action is to inhibit protein synthesis. Bacteriostatic.

II. STRUCTURAL CHARACTERISTICS

The tetracyclines consists of four fused rings, with substitutions at positions 5, 6, & 7. These analogs have different pharmacokinetic properties and are sometimes grouped into short-acting (tetracycline and oxytetracycline), intermediate-acting (demeclocycline and methacycline) and long-acting (doxycycline and minocycline).

III. SPECTRUM

a.) Gram positive cocci - Staphylococci and streptococci (except for Group D Streptococcus)
Note: resistant is significant and increasing. Minocycline may be an alternative agent for methicillin-resistant Staph. aureus in combination with rifampin.

b.) Gram negative aerobes - E. coli, Klebsiella, Enterobacter sp., Neisseria gonorrhoeae, N. meningitidis, H. influenzae - can be effective for some community acquired strains.

c.) Rickettsia, Chlamydiae, and Mycoplasmas

d.) Anaerobic bacteria esp. Fusobacterium and some Bacteroides sp. and Microaerophilic bacteria, esp. Helicobacter pylori and Campylobacter jejuni

e.) Borellia burgdorferi (Lyme disease)

f.) Pseudomonas pseudomallei, Mycobacterium marinum, Brucella sp. & Campylobacter sp., Vibrio cholerae, Erlichia, Haemophilus ducreyi (chancroid).

IV. USES

Tetracyclines are the drugs of choice for:

a.) Non-gonococcal urethritis - Chlamydia trachomatis - urethritis, cervicitis, conjunctivitis, proctitis, and lymphogranuloma venereum. Chlamydia is #1 sexually transmitted infection. Also covers other organisms that cause non-gonococcal urethritis (NGU) such as Ureaplasma urealyticum and Mycoplasma hominis
Doxycycline therapy requires 7 d vs. single dose azithromycin.

b.) Pelvic inflammatory disease – IV doxycycline with cefoxitin or cefotetan with oral switch to cefixime

c.) Atypical pneumonia and bronchitis due to Chlamydia pneumoniae (TWAR strain)
Also for Chlamydia psittaci (psittacosis and ornithosis). Will cover Mycoplasma pneumoniae, too. Resistance is relatively high for bacterial causes.

d.) Lyme disease -Borellia burgdorferi & Erlichiosis (Erlchia chaffeensis)

e.) Rickettsial disease - Rocky Mountain spotted fever, endemic typhus, Q fever, etc.
f.) *Helicobacter pylori* (combined with metronidazole and bismuth subsalicylate). *Helicobacter* have recently been implicated in peptic and duodenal ulcer disease.

g.) Other miscellaneous pathogens such as *Brucella* (with gentamicin), *Vibrio cholerae* (cholera), *Pseudomonas mallei* (with streptomycin), *Mycobacterium marinum* (minocycline), *Mycoplasma pneumoniae, Haemophilus ducreyi* (chancroid), *Erlichia*
OTHER USES

a.) **Moderate to severe acne** both by systemic treatment and by topical application

b.) Alternate drug for acute exacerbations of chronic bronchitis although use is questionable due to resistance. Useful for *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*.

c.) Alternate choice for community acquired UTIs. Resistance is a problem.

d.) Alternative drug when penicillins or cephalosporins are contraindicated for gonorrhea, syphilis, *Clostridium* species, *Actinomyces* species, *Listeria monocytogenes*

e.) Minocycline has been used for treatment of asymptomatic carriers of *N. meningitidis*. The drug should be reserved for situations in which the risk for meningococcal meningitis is high. It should **not** be used for treatment of meningococcal infection. Minocycline is also a possible alternative for MRSA.

f.) Traveler's diarrhea due to enterotoxigenic *E. coli*. (doxycycline)

g.) Prevention of malaria in mefloquine-resistant endemic areas (doxycycline)

V. RESISTANCE

Widely used as feed additives in farm animals

Tetracycline is cheap - widely and indiscriminately used in third world countries.

Resistance to enteric organisms is mediated through R-factors e.g. *Shigella*

Mechanism - preventing the accumulation of tetracycline within the cell by decreasing the influx transport system or by increasing TCN efflux. Tetracycline efflux appears to be the major mechanism.

Cross-resistance to all tetracyclines. Exceptions: *Staph. aureus* to minocycline and *B. fragilis* to doxycycline.

VI. DISPOSITION, EXCRETION, AND METABOLISM

– Widely distributed in all tissues. CSF levels ~10-20% of concentration in plasma.

– Minocycline is somewhat more lipophilic at physiological pH - reaches higher concentrations in tears and saliva - useful for meningococcal carrier state

– Accumulates in growing bone and teeth. Excreted in breast milk.

– Peak levels - 4 µg/ml after 500 mg of TCN, 2.5 µg/ml after 200 mg of doxycycline or minocycline.

– Excreted both in bile and urine. Minocycline is metabolized.
### Table 38. Pharmacokinetic Properties of Tetracyclines

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Absorption (%)</th>
<th>Half-life (hours)</th>
<th>Renal Cl (ml/min/1.73 m²)</th>
<th>% Urinary Recovery</th>
<th>Apparent Vd (liters)</th>
<th>% protein bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
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<td>Oxytetracycline</td>
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<td>9</td>
<td>99</td>
<td>70</td>
<td>128</td>
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<td>8</td>
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<td>108</td>
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<td>Intermediate</td>
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<td>Doxycycline</td>
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<td>18</td>
<td>20</td>
<td>42</td>
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<tr>
<td>Minocycline</td>
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<td>16</td>
<td>9</td>
<td>6</td>
<td>60</td>
<td>76</td>
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</tbody>
</table>

### VII. ADVERSE EFFECTS

a.) Teeth and Bones - gray-brown to yellow permanent discoloration of teeth in 80% of children. Effect on tooth enamel related to exposure. Depression of skeletal growth in premature infants. **Not recommended for children <8 or pregnant or nursing women.**

b.) GI upset. This is quite common. Nausea, vomiting, and epigastric distress are dose related. May give minocycline or doxycycline with food, but not others.

c.) Diarrhea. Common with tetracycline and oxytetracycline. Rare *C. difficile* colitis.

d.) Vertigo (light-headedness, dizziness, tinnitus, loss of balance) with **minocycline** only. Occurs in ~70% of women, 28% of men.

e.) Photosensitivity especially with **demeclocycline**. Others may also cause this. Incidence low with minocycline.

f.) Rare hypersensitivity reactions, serum-sickness like reactions, drug-induced lupus, hepatic injury, or nephrotoxicity. Hepatic injury associated with large IV tetracycline doses of >2g/day has resulted in death. When used chronically for dermatologic problems, **minocycline** produces more serious adverse effects (especially hypersensitivity syndrome, drug-induced lupus, & serum-sickness like reactions) than tetracycline or doxycycline. Ref: Arch. Dermatol. 133:1224-30 (1997).
VIII. PRODUCTS

**Tetracycline**  
Capsules and tablets: 250 mg and 500 mg  
Oral suspension: 125 mg/ml  
Powder for IM or IV injection: (100, 250, or 500 mg).

Usual adult dose: 1-2g per day divided in 2 to 4 equal doses.

**Demeclocycline** - Declomycin® (Lederle)  
Capsules: 150 mg  
Tablets: 150 and 300 mg

Adults: 4 divided doses of 150 mg or 2 doses of 300 mg per day

**Methacycline** - Rondomycin® (Wallace)  
150 and 300 mg capsules

Adults: 300 mg b.i.d. or 150 mg q.i.d.

**Doxycycline** - Vibramycin® (Pfizer)  
Capsules and tablets: 50 & 100 mg  
Suspension: 25 mg/ml  
Syrup: 50 mg/ml  
Powder for injection: 100 & 200mg

Adults: 100mg b.i.d. (first day), then 100 mg daily

**Minocycline** - Minocin® (Lederle) –  
Capsules, pellet filled: 50 & 100 mg (Minocin®)  
Tablets and capsules: 50 & 100 mg (various manufacturers)  
Oral Suspension: 50 mg/ml  
Powder for Injection: 100 mg

Adults: 200 mg initially, then 100 mg every 12 hours

Patient Instructions for Tetracyclines

1. Take tetracycline or demeclocycline on an empty stomach. Take with a full glass of water  
(Note: doxycycline or minocycline may be taken with food).

2. Avoid simultaneous dairy products (milk, cheese, yogurt), antacids, laxatives, or iron-containing products. Tetracycline complexes with divalent cations (Mg, Ca, Fe) to form an insoluble complex.

3. Avoid prolonged exposure to sunlight or sunlamps especially with demeclocycline.