CLINDAMYCIN, METRONIDAZOLE, CHLORAMPHENICOL

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CLINDAMYCIN

I. CLASSIFICATION AND HISTORICAL INFORMATION
   A. Derivative of lincomycin
   B. Has replaced lincomycin as agent in its own category
II. MAIN INDICATIONS
   A. Anaerobic Infections (gram-positive and gram-negative). Exception: *Clostridium difficile*
   B. Mixed aerobic/anaerobic infections (when combined with other agents)
   C. Alternative agent for gram-positive cocci. Exception: not MRSA, MRSE or enterococcus
   D. Select parasitic infections (i.e., AIDS patients)
   SPECIAL NOTE: not indicated for gram-negative aerobic infections
III. MAIN PROPERTIES AND ADVANTAGES
   A. Bacteriostatic agent
   B. Good half-life (2.4 hours)
   C. Excellent tissue distribution and penetration (except CSF)
   D. Parenteral (I.M., I.V.), oral or topical administration
   E. Liver metabolism: renal and biliary excretion
   F. Can be combined and mixed with aminoglycosides in the same solution
IV. DISADVANTAGES
   A. No activity against gram-negative aerobic bacteria
   B. No activity against *Clostridium difficile*
   C. Limited activity against *Bacteroides fragilis* (5-20% of these organisms are resistant)
V. TOXICITY AND ADVERSE EFFECTS
   A. *Clostridium difficile* toxin-mediated pseudomembranous colitis (most notorious but not the most significant)
   B. GI side effects: nausea, anorexia, vomiting, and diarrhea
   C. Hematologic changes
   D. Allergic reactions
   E. Neuromuscular blockade
VI. DOSAGE SCHEDULE AND PHARMACOLOGIC PROPERTIES
   A. Oral administration: 150-300 mg q6h
   B. Parenteral administration (I.M. or I.V.): 600-2,700 (more) mg/day in 3 or 4 equal doses
   C. Decrease dose by 1/2 in patients with severe renal insufficiency or severe hepatic disease with renal failure
VII. PSEUDOMEMBRANOUS COLITIS
   A. Organism: *Clostridium difficile*
   B. Toxin-mediated entity
   C. Most cases are associated with penicillins and cephalosporins (not clindamycin)
   D. Variable incidence
   E. Diagnosis
      1. Stool cultures (high sensitivity: variable rate of false positives)
      2. Cytotoxin assay (highly specific but of moderate sensitivity)
   F. Treatment
      1. Discontinue precipitating agent

2. Administer oral vancomycin or metronidazole
3. Supportive therapy (fluids, electrolytes, etc.)

VIII. SUMMARY
- A. Potentially a useful agent, especially for anaerobic infections (except *Clostridium difficile*) or mixed aerobic-anaerobic infections
- B. Is an alternative third-line agent for gram-positive infections (exceptions: MRSA, MRSE or Enterococci)
- C. No clinical usefulness for gram-negative aerobic infections

METRONIDAZOLE (FLAGYL)

I. CLASSIFICATION AND HISTORICAL INFORMATION
- A. Sole agent - in its own category

II. MAIN INDICATIONS
- A. Parasitic infections
  1. Trichomonas vaginitis
  2. Giardiasis
  3. Amebiasis
- B. Anaerobic infections (excellent for podiatric use)
  1. Gram-positive bacteria
     a. Peptococci (limited activity)
     b. Peptostreptococci (limited activity)
     c. *Clostridium perfringens*
     d. *Clostridium difficile*
  2. Gram-negative bacteria
     a. *Bacteroides fragilis*
     b. Other bacteroides species
     c. Fusobacteria
- C. *Clostridium difficile* associated pseudomembranous colitis

III. MAIN PROPERTIES AND ADVANTAGES
- A. Bacteriostatic agent
- B. Excellent half-life (8 hours)
- C. Tissue distribution and penetration
- D. Parenteral or oral administration

IV. DISADVANTAGES
- A. Limited activity against some anaerobic gram-positive cocci (i.e., Peptococci and Peptostreptococci)
- B. Clinical usefulness limited to anaerobic infections in podiatry
- C. Not effective against aerobic gram-positive and gram-negative organisms

V. TOXICITY AND ADVERSE EFFECTS
- A. GI system: nausea primarily (especially with the oral form), epigastric discomfort or diarrhea
- B. Reversible neutropenia
- C. Cutaneous eruptions
- D. Metallic taste
- E. Convulsive seizures and peripheral neuropathy (rare)
- F. Disulfiram-like effect with alcohol consumption

VI. Dosage Schedule and Pharmacologic Properties
- A. Intravenous administration
  1. Loading dose: 15 mg/kg
  2. Subsequent doses: 7.5 mg/kg q6h
- B. Oral administration: 1-2 gm/day in 2-4 divided doses
- C. No adjustment with renal failure unless creatinine clearance is < 10 ml/min
- D. Reduce dosage in patients with severe hepatic disease
- E. Antacids, barbiturates, and cholestyramine decrease serum concentrations of the drug

VII. SUMMARY
- A. Very useful agent in podiatry for the management of both gram-positive and gram-negative anaerobic infections
- B. Very useful agent in the management of *Clostridium difficile* associated pseudomembranous colitis
- C. A very safe drug

CHLORAMPHENICOL

I. CLASSIFICATION AND HISTORICAL INFORMATION
- A. Sole agent - in its own category
- B. Introduced approximately 42 years ago - mostly an agent of historical footnote status today

II. MAIN INDICATIONS
- A. Few if any indications in podiatry; primarily of historical interest
- B. Serious infections caused by *Salmonella* species, *H. influenzae*, and Rickettsia, especially when other agents (penicillin, cephalosporins, tetracycline) CANNOT be used
- C. This agent has essentially been replaced by many other more useful and practical agents

III. MAIN PROPERTIES AND ADVANTAGES
- A. Bacteriostatic agent
- B. Variable half-life (1.6-4.1 hours)
- C. Good tissue distribution and penetration.
- D. Can be parenteral (I.V.) or oral administration (capsules and suspension form)
- E. Effective against most aerobic gram-positive bacteria (not MRSA, MRSE; variable effectiveness against Enterococcus)
- F. Most gram-negative bacteria (exceptions: *Klebsiella*, *Enterobacter*, *Serratia*, *Acinetobacter*, and *P. aeruginosa*)
- G. Effective against most anaerobic gram-positive and gram-negative bacteria
- H. Liver metabolism/renal excretion

IV. DISADVANTAGES
- A. Associated serious toxicity
- B. Not a major first-line drug or agent for anything
- C. Minimal to no usefulness in podiatry
- D. Although effective against many gram-positive and gram-negative organisms, it is not effective against clinically important organisms

V. TOXICITY AND ADVERSE EFFECTS
- A. Idiosyncratic bone marrow aplasia
  1. Unpredictable
  2. Incidence: 1:24,200 to 1:40,500
  3. Occurs weeks to months after completion of the antibiotic administration
  4. Pancytopenia is most common; irreversible and typically fatal
- B. Reversible bone marrow depression
  1. Dose related (> 4 gm/day or 25 Ig/ml serum levels)
  2. May present as anemia, leukopenia or thrombocytopenia
- C. "Gray baby" syndrome
  1. Occurs in premature infants and newborns
  2. Rare but potentially fatal
  3. Characterized by abdominal distention, cyanosis, and vasomotor collapse

VI. DOSAGE SCHEDULE AND PHARMACOLOGIC PROPERTIES
- A. Dosage in adults: 50-100 mg/kg/day in 3 or 4 divided doses. NOTE: avoid I.V. administration
- B. Dosage in children and neonates (refer to PDR)
- C. Serum concentration should be monitored closely in patients with hepatic dysfunction (10-30 g/ml is recommended)
- D. In patients with renal impairment alone, no appreciable accumulation is detected
- E. Reduced doses imperative in patients with hepatic disease; not necessary for patients with renal insufficiency alone
- F. Caution with other concomitant drugs
  1. Phenobarbital, rifampin, and phenytoin cause increased metabolism of the drug (and therefore, decreased activity)
  2. May cause increased (toxic) levels of accumulated hypoglycemic agents, phenytoin, cyclophosphamide, and warfarin

VII. SUMMARY: not a very useful agent