ORAL ANTIBIOTICS

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Oral antibiotics are often preferred to parenteral (intramuscular/intravenous) compounds because of their safety, convenience, and economy. Use of an oral agent can preempt a hospitalization. The most appropriate antibiotic is one that is safe, inexpensive, effective, and resolves the infection. Specific guidelines and indications must be addressed when considering the oral route of delivery. Failure to follow these guidelines can result in ineffective treatment of an infection. This paper will outline the mechanism for selection of an appropriate oral agent.

The most important factor to consider when choosing an antibiotic is the sensitivity of the organism for the particular agent. All other things being equal, the preferred agent is the one that can kill the organism in the lowest concentration (greatest sensitivity). Antibiotics are compared by their minimum inhibitory concentration (MIC). The MIC is defined as the least amount of antibiotic that will inactivate, but not necessarily kill, the microorganism in question. An acceptable MIC is one that is 25-50 percent of achievable serum levels. This must be considered especially when you are counting on oral absorption. Whenever possible, the antibiotic with the lowest MIC should be chosen to maximize inhibition.

Additional considerations when selecting an antibiotic include complicating health conditions, ease of administration, compliance, toxicity, drug allergies and cost of the agent. When considering the oral route as opposed to the parenteral route, additional factors must be addressed.

The most critical concerns are absorption of the drug from the gastrointestinal tract and patient compliance. The restrictions associated with the use of oral antibiotics are clearly related to inadequate absorption of the agent. Major concerns include emesis of the drug, drug inactivation by gastric acid and digestive enzymes, and irregular absorption. Even if the drug makes it to the absorption surface in sufficient concentrations, inadequate amounts may be absorbed. Absorption of a drug is effected by relative surface area, blood flow to the area, physical state of the drug and concentration of the drug. Gastric emptying time can control the relative surface area available for absorption. A delay in emptying time from the stomach can keep the drug away from the larger surface area of the small intestine. In general, the larger the surface area, the higher the blood levels of the antibiotic. Retention of stomach contents is often seen in stress (infection, trauma, and preoperatively) and chronic disease states (ie. diabetes, Rheumatoid arthritis). Similarly, a decrease in blood flow to the gastrointestinal tract may be observed in those situations. Decreased perfusion will again result in a decreased serum concentration.

Patient compliance becomes more of a factor when utilizing the oral route. Maintenance of proper levels can only be obtained if the patient cooperates. Careful monitoring of levels must be preformed to assure the preservation of adequate concentrations. Factors which effect patient compliance include cost, convenience of dosing, size and amount of the dose, taste and side effects. The importance of these factors will vary from patient to patient. Therefore, consideration must be given to all of these distractions prior to prescribing a particular agent.

Cost is a major concern to most patients. The cost of different antibiotics for the treatment of the same infection can vary tremendously. Newer drugs, which tend to be more expensive, may not even be as effective as their older counterparts. Additionally, expensive broad spectrum antibiotics are usually unnecessary when a single organism is isolated. One should choose an agent which is effective and inexpensive.

Oral antibiotics should be dosed on an around-the-clock schedule. An agent that needs to be dosed every six hours must be given at those intervals. Delivery of the drug four times a day during waking hours will result in erratic blood levels and may result in prolonged infection or possible bacterial resistance. Problems with compliance can develop when dosing around-the-clock (q 6 h) is necessary. However, studies have shown this not to be a problem if the importance of proper timing has been carefully explained to the patient. A drug should not be selected based only on ease of dosing especially if sacrificing drug sensitivity. Additionally, if the dosing schedule is easier (every twelve hours compared to six hours) but the price too high, the patient may never have the prescription filled.

The market is crowded with antimicrobial agents available for oral use. A brief review of commonly used antibiotics will be discussed with regards to spectrum, pharmacokinetics and untoward effects.

PENICILLINS

Three classes of penicillin are utilized to treat gram positive soft tissue and bone infections. (Table 1) The natural penicillins have a limited role in treating soft tissue infections. They are ineffective against most Staphylococcal infections and are usually reserved for uncomplicated *Streptococcus pyogenes* infections. Penicillin VK is the preferred choice because of its better absorption.

Table 1

ORAL PENICILLINS

Natural Penicillins
- Penicillin G
- Penicillin V

Penicillinase-Resistant Penicillins
- Oxacillin
- Cloxacillin
- Dicloxacillin

Aminopenicillins
- Ampicillin
- Amoxicillin

Penicillin Combined with Beta-lactamase Inhibitor
- Amoxicillin/Clavulanate (Augmentin)

The penicillinase resistant penicillins (PCP) are widely used in the treatment of outpatient infections. High serum levels combined with low MICs make them one of the drugs of choice against nonmethicillin resistant *Staphylococcus aureus*. The only drawback is their short half life which requires dosing every six hours.

The aminopenicillins have a limited role in podiatric medicine. They offer a slight increase in gram negative coverage while sacrificing *S. aureus* sensitivity. Amoxicillin is the preferred compound because of its increased absorption. The addition of clavulanate has increased amoxicillin's effectiveness against *S. aureus*. Clavulanate is a betalactamase enzyme inhibitor with no antibacterial action of its own. Amoxicillin-clavulanate (Augmentin) has been useful in treating skin infections of Staphylococcus and Streptococcus. In addition, it is an excellent choice in the empiric treatment of mild diabetic foot infections.

The penicillins differ markedly in their rate of oral absorption. Penicillin G is very poorly absorbed and is extremely unstable to gastric acids. Penicillin V and most of the synthetic penicillin are readily absorbed following oral administration. Peak serum levels of most penicillins are obtained in one to two hours after ingestion. A delay of two to three hours can occur when ingested with food.

The most common untoward effects associated with the penicillins are allergic reactions. The response can span from a mild rash to an immediate anaphylaxis. True anaphylaxis is relatively uncommon occurring in 0.2 percent of 10,000 cases. Other untoward responses have been rare and self-limiting including GI irritation, pseudomembranous enterocolitis and neutropenia.

CEPHALOSPORINS

The cephalosporins are traditionally classified into first, second and third generations. Progressing from first to third generations, the compounds have increased activity against gram negative organisms, while inhibition of gram positive organisms decreases. Oral cephalosporins, including third generation compounds, have not shown to be active against *Bacteroides fragilis* or *Pseudomonas aeruginosa*. Currently, there are three first generation, two second generation and one third generation cephalosporins available for oral

use. (Table 2) Only the first and second generation oral cephalosporins have displayed a role in the treatment of lower extremity infections.

In general, the cephalosporins are well absorbed following ingestion. Although absorbed with food, between-meal dosing enhances absorption. Good peak serum levels are obtained quickly after administration. Serum half-life varies between the compounds allowing for extended dosing intervals with certain compounds. The oral cephalosporins are excreted predominately in the urine. Therefore, patients with suspected renal insufficiency should have their dosages properly adjusted.

Cross-sensitivity in patients allergic to penicillin is a potential risk associated with the use of all cephalosporins. Cross-reactivity with the penicillins has been reported in varying degrees. If the patient experienced an immediate or accelerated immune reaction following the administration of penicillin, treatment with a cephalosporin should be avoided. However, if the patient experienced a delayed response, rash or GI complaints, cephalosporins can be utilized with caution. The cephalosporins are relatively safe drugs. Untoward reactions associated with the administration of cephalosporins are limited to infrequent, mild, self-limiting events, such as GI irritation, fever and rashes.

The first generation cephalosporins have been successful in the treatment of uncomplicated Staphylococcal and Streptococcal soft tissue infections. Cephalexin and cefadroxil have been extremely effective because of their high serum levels and low MIC's. Excellent osseous and synovial penetration has permitted them to be used in the pediatric population for the treatment of *S. aureus* osteomyelitis.

The second generation cephalosporins possess the added dimension of limited gram negative coverage including *Klebsiella, E. coli,* and *P. vulgaris*. The coverage does not include *P. aeruginosa* and therefore, limits their role in the treatment of Gram negative foot infections. Cefuroxime axetil, a prodrug, is converted to cefuroxime in the body. Good *S. aureus* coverage combined with an extended dosing time make it a potential choice. Cefprozil, another second generation cephalosporin, has shown to be effective in the treatment of cellulitis and impetigo.

Table 2

ORAL CEPHALOSPORINS

First Generation
- Cephalexin (Keflet, Keflex, Keftab)
- Cephradine (Anspor, Velosef)
- Cefadroxil (Duricef, Ultracef)

Second Generation
- Cefaclor (Ceclor)
- Cefprozil (Cefzil)
- Cefuroxime axetil (Ceftin)

Third Generation
- Cefixime (Suprax)
- Cefpodoxime proxetil (Vatin)

QUINOLONES

The fluorinated quinolones continue to grow as a group since being introduced. Currently, there are five compounds available for use. (Table 3) Ciprofloxacin, has demonstrated the greatest effectiveness in treating soft tissue and bone infections.

The fluoroquinolones are all well absorbed following oral administration, achieving good peak serum concentrations one to five hours after administration. Low serum protein binding allows greater concentrations of the antibiotic at extravascular sites. The drug is administered every twelve hours because of a prolonged serum half life.

The concomitant use of compounds containing aluminum, magnesium or zinc can reduce the oral absorption by 60 to 90 percent. Also the use of sucralfate (Carafate) for the treatment of gastric or duodenal ulcers can reduce absorption.

Table 3

QUINOLONES

Ciprofloxacin (Cipro)
Enoxacin (Penetrex)
Lomefloxacin (Maxaquin)
Norfloxacin (Noroxin)
Ofloxacin (Floxin)

An important drug interaction between the fluoroquinolones and theophylline should be avoided. The quinolones have been shown to increase serum concentrations of theophylline producing potentially harmful levels. Patients should also be cautious about caffeine intake while on quinoline therapy. Symptoms of restlessness, insomnia, and other CNS dysfunctions have been observed following combined use.

The most common untoward reaction associated with the fluroquinolones is gastrointestinal irritation. Dizziness, insomnia, and headaches have also been documented in patients taking the fluoroquinolones. Alterations in laboratory values, such as elevation of liver enzymes, neutropenia, leucopenia, and eosinophilia, can occur in patients taking these antibiotics. Fluoroquinolones are contraindicated in patients less then 18 years of age. The quinolones have been shown to cause damage to immature cartilage in laboratory dogs.

Ciprofloxacin exhibits good activity against a wide variety of aerobic gram positive and negative organism. Anaerobes such as *B. fragilis* are poorly covered. *P. aeruginosa* is fairly well covered by ciprofloxacin. Methicillin resistant *S. aureus* continues to increase resistance to the fluoroquinolones as a group.

Due to high serum levels and bone concentrations, ciprofloxacin can be utilized for skin, soft tissue, joint and bone infections. Bone infection with a variety of organisms including *P. aeruginosa* has been effectively treated by ciprofloxacin. However, more comparative studies between ciprofloxacin and currently accepted agents for the treatment of osteomyelitis are necessary.

MACROLIDES/CLINDAMYCIN

Although chemically unrelated, the macrolides and clindamycin share similar biological properties in terms of mechanism of action, antimicrobial activity and clinical pharmacology. (Table 4) The macrolides and clindamycin have few primary indications and serve mainly as a backup to patients allergic to penicillin. They both have good activity against staphylococcal and streptococcal infections. In addition, clindamycin has excellent coverage against anaerobic infections including *B. fragilis*.

Erythromycin is available in four oral forms: base, stearate, ethylsuccinate, and estolate. All

Table 4

MACROLIDES

Azithromycin (Zithromax)
Clarithromycin (Biaxin)
Erythromycin

forms are fairly well absorbed from the stomach. Food affects the absorption of all but the estolate form. Enteric coating of erythromycin base has increased the absorption and decreased the GI side effects associated with the administration. Peak serum concentrations are obtained four hours after oral administration. The half life is relatively short, requiring dosing every six hours. Erythromycin is one of the safest antibiotics. GI irritation continues to be the only problem with its use.

Two new macrolides have recently been approved by the US Food and Drug Administration: clarithromycin (Biaxin) and azithromycin (Zithromax). Both have activity similar to erythromycin. The advantage of these compounds over erythromycin is their improved tissue penetration. This allows high concentrations of the drug within tissue and cells, particularly macrophages and polymorphonuclear leucocytes.

Clindamycin is 90% absorbed after oral administration and is not affected by food. Peak serum concentrations are obtained one to two hours after oral ingestion. The concern with the use of clindamycin is the potential for GI irritation. GI upset is associated with its use in 2-20% of the patients. Although the occurrence of pseudomembranous colitis is possible with the administration of any antibiotic, it is seen in up to 10 percent of the patients taking clindamycin.

CARBACEPHEMS

The carbacephems are a new class of beta-lactam antibiotics which are similar in structure to the cephalosporins. Currently, only one of these compounds is available, loracarbef (Lorabid), for the treatment of skin and soft tissue infections. Loracarbef is similar in activity to the second generation cephalosporins. The compound has been shown to have effective activity in the treatment of infections caused by *Staphylococcus aureus*. Loracarbef has been found to be ineffective

against methicillin-resistant *Staphylococcus aureus,* Pseudomonas species and *Bacteroides fragilis.* The most common adverse effect associated with loracarbef is diarrhea. Patients allergic to penicillin may also be allergic to loracarbef because of its beta-lactam structure.

SKIN AND SOFT TISSUE INFECTIONS

The majority of soft tissue infections in podiatric medicine are caused by a gram positive organism. Non-methicillin resistant *S. aureus* accounts for about 90 percent of these infections. Treatment of mild to moderate infections can be successful with oral antibiotics. Severe infection or sepsis usually requires initial treatment with an intravenous antibiotic until control of the infection is obtained. Appropriate coverage of *S. aureus* infection includes the use of a penicillinase resistant penicillin or a first generation cephalosporin. The drug of choice in patients without true penicillin allergy is dicloxacillin. Adults should receive 250-500 mg every six hours for 10-14 days depending on the severity of the infection. Pediatric infections should be treated with 25-100 mg/kg/day divided into four equal doses delivered every six hours. Cephalexin, cefadroxil, and cefuroxime axetil are good alternative choices.

Patients who have exhibited an anaphylactoid reaction to penicillin, can be placed on macrolide or clindamycin. Erythromycin can be given 250-500 mg every six hours for adults. Azithromycin's convenient dosing schedule makes it an excellent alternative. A dose of 500 mg of azithromycin is given the first day followed by 250 mg for the next four days. Clindamycin 150-300 mg every six hours is a good alternative, especially if anaerobes are suspected in the infection.

Isolated aerobic streptococcal infections can be managed with penicillin VK 125-500 mg or 50 mg/kg/day divided into four doses every six hours. Erythromycin can be substituted for those allergic to penicillins.

Ciprofloxacin should not be utilized in isolated Staphylococcus or Streptococcal soft tissue infections. The Beta-lactams, erythromycin and clindamycin are the preferred compounds in these infections. Infections caused by MRSA can be treated with caution with ciprofloxacin in combination with another compound. In the past, MRSA infections required parenteral antibiotics such as vancomycin. The dose for ciprofloxacin is 500-750 mg every twelve hours for 10-14 days.

In addition, infections involving both gram positive and negative organisms can be treated with ciprofloxacin, obviating the need for parenteral antibiotics. Amoxicillin and clavulanate (Augmentin) can also be used in mixed infections because of its activity against *Staphylococcus aureus,* anaerobes and gram negative aerobes.

BONE AND JOINT INFECTIONS

Traditionally, bone and joint infections were treated with intravenous antibiotics for the entire course of therapy. Recent literature has shown encouraging results when placing the patient on oral antibiotics after a short course of parenteral drugs. Some papers have even shown complete eradication following oral therapy alone.

The cornerstone of treatment of any bone or joint infection is adequate debridement. The choice of route of antibiotic will then depend basically on how much antibiotic is necessary. In the infection of bone and joints, most prefer to obtain concentrations 5-10 times the MIC. Many times, this concentration is unobtainable by the oral route. The antibiotic therapy should then be initiated by parenteral route. The pediatric population has demonstrated extremely high serum levels of dicloxacillin and cephalexin in studies and may be the exception. The universal use of oral antibiotics in the treatment of osteomyelitis should be limited until further literature has proven their efficacy.

Oral antibiotics have a role in the long term therapy of bone and joint infections. Six weeks of antibiotics are usually required to treat osteomyelitis. Two to four weeks of parenteral antibiotics followed by oral drugs for the remainder have proven to be effective in eradication. Combinations of oral and parenteral compounds have improved outpatient treatment of bone and joint infections. A precise discussion on the utilization of oral compounds for the treatment of bone and joint infections is beyond the scope of this paper.

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