ORAL ANTIBIOTICS

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Oral antibiotics are often preferred to parenteral (intramuscular/intravenous) compounds because of their safety, ease of administration, and economics. Obviously, utilization of an oral agent can obviate the need for hospitalization. The most appropriate antibiotic is one that safely, inexpensively, and effectively promotes resolution of 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 in choosing 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 organism in question. An acceptable MIC is one that 25-50% of the achievable serum levels. This is very important especially when one is counting on oral absorption. Whenever it is possible the antibiotic with the lowest MIC should be chosen to maximize inhibition.

Additional factors to contemplate 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 elements 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 are emesis of the drug, drug destruction by gastric acid or digestive enzymes, and irregular absorption. Even if the drug makes it to the absorption surface in sufficient concentrations, inadequate amounts may be absorbed to achieve suitable blood levels of the antibiotic. Absorption of a drug is also affected by relative surface area, blood flow to the area, physical state 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. A decreased emptying time is often seen in stress (infection, trauma, and preoperatively) and chronic disease states (i.e., diabetes, Rheumatoid arthritis). Similarly a reduced blood flow to the gastrointestinal tract may be observed in those situations, again eventually impacting upon serum concentrations of the agent.

Patient compliance becomes more of a factor when utilizing the oral route. Maintenance of proper levels can be obtained only if the patient cooperates. Careful monitoring of levels must be preformed to assure the preservation of adequate concentrations. Factors which affect 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 to treat the same infection can vary tremendously. A relative comparison of oral agents effective in the treatment of a S. aureus soft tissue infections is presented in Table 1. Newer drugs, which tend to be more expensive, may not even be as effective as the 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 preferably inexpensive.

Table 1

ORAL PENICILLINS

Natural Penicillins
- Penicillin G
- Penicillin V

Penicillinase-Resistant Penicillins
- Oxacillin
- Cloxacillin
- Dicloxacillin

Aminopenicillins
- Ampicillin
- Amoxicillin

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 prolong the infection or possibly create bacterial resistance. Problems with compliance can develop when dosing around the clock every six hours is necessary. However, studies have shown this not to be a problem if the importance of proper times has been carefully explained to the patient. A drug should not be selected based only on ease of dosing, especially if one is 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 encumbered with antimicrobial agents available for oral use. A brief review of commonly used antibiotics with regards to spectrum, pharmacokinetics, and untoward effects will be discussed.

PENICILLINS

Three classes of penicillin are utilized to treat gram positive soft tissue and bone infections.(Table 2) The natural penicillins have a limited role in treating soft tissue infections. They are ineffective against most Staphylococcal organisms and are usually reserved for treatment of uncomplicated Streptococcus pyogenes infections. Penicillin VK is the preferred choice due to its better absorption.

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 non-methicillin 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 due to its absorption profile. 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 infection of Staphylococcus and Streptococcus.

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

Table 2

COST COMPARISON FOR ANTIBIOTICS EFFECTIVE IN TREATING S. AUREUS SOFT TISSUE INFECTIONS. (10 DAY COURSE OF THERAPY)

ANTIBIOTIC (BRAND NAME)	DOSAGE	AVERAGE WHOLESALE COST TO PHARMACY
DICLOXACILLIN (DYNAPEN)	250mg.q6h.	9.34
		37.60
	500mg.q6h.	16.57
		70.24
CEPHALEXIN (KEFLEX)	250mg.q6h.	5.60
		35.68
	500mg.q6h.	11.20
		70.00
CEFADROXIL (DURICEF, ULTRACEF)	500mg.q12h.	N/A
		42.09
	1gm.q12h.	N/A
		79.95
CEFUROXIME AXETIL (CEFTIN)		
	250mg.q12h.	N/A
		43.92
	500mg.q12h.	N/A
		83.35
CLINDAMYCIN (CLEOCIN)	150mg.q6h.	28.60
		40.49
	300mg.q6h.	N/A
		76.90

The most common untoward effect associated with the penicillins are allergic reactions. The response can span from a mild rash to an immediate anaphylaxis. True anaphylaxis is a relatively uncommon occurrence, presenting 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 organism, while inhibition of gram positive organisms decreases. Oral cephalosporins 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 cephalosporin available for oral use.(Table 3) Only the first and second generation oral cephalosporins have displayed a role in the treatment of lower extremity infections.

Table 3
ORAL CEPHALOSPORINS

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

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

Third Generation
- Cefixime (Suprax)

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 agents. Excretion is predominately via the urine. Therefore, patients suspected of 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 penicillin 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 experiences a delayed response, rash or GI complaints, a cephalosporin can be utilized with caution.

The cephalosporins are relatively safe drugs. Untoward reactions associated with the administration of cephalosporin 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 has been extremely useful due to its high serum levels and low MIC. Excellent osseous and synovial penetration has permitted cephalexin to be used in pediatric population for the treatment of S. aureus osteomyelitis.

The second generation cephalosporin 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 its benefit to podiatric 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. However, the compound is quite expensive and is not available in a liquid form.

QUINOLONES

The quinolones are a relative new group of antibiotics that have shown good activity when used orally. Currently, ciprofloxacin, a fluorinated quinolone, has demonstrated the most effectiveness in treating soft tissue and bone infections. The compound is 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 use of aluminum or magnesium-containing compounds can reduce the oral absorption of ciprofloxacin by 60 to 90 percent. Also, the utilization of H2 inhibitors for the treatment of gastric or duodenal ulcers can reduce absorption. An important drug interaction between ciprofloxicin and theophylline should be avoided. The quinolones have been shown to inhibit the metabolism of theophylline producing potentially harmful levels. Patients should also be careful of caffeine intake while on quinolone therapy. Symptoms of restlessness, insomnia, and other CNS dysfunctions have been observed following combined use. The most common untoward reaction associated with ciprofloxacin is gastrointestinal irritation. Dizziness and headaches have also been documented in patients taking ciprofloxicin. An alteration in laboratory values such as elevation of liver enzymes, neutropenia, leucopenia, and eosinophilia, can occur in patients taking this antibiotic.

Ciprofloxacin use is contraindicated in the patient less than 18 years of age. The quinolones have shown to cause damage to immature cartilage in laboratory animals.

Ciprofloxicin exhibits good activity against a wide variety of aerobic gram positive and negative organisms. Anaerobes such as B. fragilis are poorly covered. Methicillin resistant S. aureus (MRSA) and P. aeruginosa are fairly well covered by ciprofloxicin. However, recent studies and observations have shown an increased incidence of resistance to ciprofloxicin by MRSA.

Due to high serum levels and adequate bone concentrations, ciprofloxicin can be utilized for skin, soft tissue, joint and osseous infections. Bone infection with various organisms including P. aeruginsosa has been effectively treated by ciprofloxicin. However, more comparative studies between ciprofloxacin and current more widely accepted agents in the treatment of osteomyelitis are necessary.

ERYTHROMYCIN/CLINDAMYCIN

Although chemically unrelated, erythromycin and clindamycin share similar biological properties in terms of mechanism of action, antimicrobial activity and clinical pharmacology. Erythromycin 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 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 currently in use. GI irritation continues to be the only problem with its oral administration.

Clindamycin is 90 percent absorbed after oral administration and is not affected by food intake. 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 percent 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 on clindamycin.

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 infections or sepsis usually requires initial treatment with an intravenous antibiotic until control of the infection is obtained. Appropriate coverage of S. aureus infections includes the use of a penicillinase resistant penicillin or a first generation cephalosporin. The preferred drug would be dicloxacillin in patients without true penicillin allergy. Adults should receive 250-500mg every six hours for 10-14 days depending on the severity of the infection. Pediatric infections should be treated with 25-100mg/kg/day divided into four equal doses delivered every six hours. Cephalexin 500mg every six hours or 25-50mg/kg/day every six hours would be an alternate choice.

Patients exhibiting anaphylaxis to penicillin could be placed on erythromycin or clindamycin. Erythromycin 250-500mg every six hours for adults. Clindamycin 150-300mg every six hours is a good alternate, especially if anaerobes are suspected in infection.

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

Ciprofloxicin 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. However, infections caused by MRSA can be treated with ciprofloxicin. In the past, MRSA infections required parenteral antibiotics such as vancomycin. The dose ciprofloxicin is 500-750mg every twelve hours for 10-14 days.

In addition, infections involving both gram positive and negative organisms can be treated with ciprofloxicin, 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 whole course of therapy. Recent literature has shown encouraging results in placing the patient on oral antibiotics after a short course of parenteral drugs. Some papers have even shown thorough eradication following oral therapy alone. The cornerstone of treatment of any bone or joint infection is adequate debridement. The selection of the route of dosing an antibiotic will then depend basically how much antibiotic is necessary. In infections of bone and joints most prefer to obtain concentrations 5-10 times the MIC. Many times this concentration is unobtainable by the oral route. 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 is usually required to treat osteomyelitis. Two to four weeks of parenteral antibiotics followed by oral drugs for the remainder of drug therapy has 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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