MustansiriyahUniversity
College of Dentistry
Endodontics lectures
5th year

Pharmacology for Endodontics

أ.د. بلند محمد سليم شكري

Infections concur with many endodontic conditions. Accordingly, it behooves the practitioner to be well prepared to use drugs that help fight infection. Unfortunately, **pain** has also become associated with endodontics, at least in the public's mind. Fortunately, for both pre- and postoperative pain, relief through drugs is readily available. In addition to pain, **anxiety** about endodontic treatment is also rampant. Again, modern antianxiety drugs have been developed, displacing the sedatives, hypnotics, and soporifics often misused to control anxiety in the past. In the present-day pharmacy, drugs are available that work directly against anxiety without many of the side effects, making dental treatment easier for the patient and the practitioner alike, enabling more patients to receive optimal dental care.

Infection control

For many years, endodontists suspected bacteria as the pathogens in necrotic pulps but were not able to prove the point because of inadequate culture methods. After the development of anaerobic culture techniques, however, investigators were able to show nearly 100% infections of necrotic pulps.

One of the primary goals of endodontic treatment is to eliminate a hospitable place for microorganisms to grow. Débridement of the canal soft tissues and debris should be as thorough as possible. The space should be totally obturated to isolate any remaining tissue from the body and to close off that path for oral bacteria to reach beyond the apex. Sterile technique should be used throughout the procedures to avoid introducing any new microbes into the patient. Attention to proper technique also protects the entire staff from receiving pathogens from the patient.

Periapically, bacteria do not usually hold the advantage, and infection is less likely. Without a doubt, situations occur where chronic infections persist in the periapex following root canal therapy.

Antibiotics

Antibacterial agents, commonly called **antibiotics**, are very useful because they kill bacteria without damage to the host. These drugs attack cell structure and metabolic paths unique to bacteria and not shared with human cells. Systemic antibiotics are used frequently in the practice of medicine and dentistry. Some say they are overused. Although this is probably true, it is also difficult to tell when an infection might spread to cause life-threatening problems, such as cavernous sinus thrombosis, Ludwig's angina, danger-space swelling reaching into the mediastinum, brain abscess, or endocarditis, all of which have developed as sequelae of root canal therapy. It is probably wise to use systemic antibiotics when there is a reasonable possibility of microorganisms beyond the root canal. The immunologically compromised patient should also be considered an indication for antibiotic therapy, regardless of the condition of the canal.

This discussion of antibiotics will not include parenteral- use drugs or drugs used rarely in dental patients, which need monitoring by a physician because of potential side effects. The dental practitioner should be acutely aware of signs of infection not responding to oral antibiotic therapy and be speedy in referring such patients to an infection specialist.

Classification

Antibiotics may be classified into two main categories: those that kill bacteria rapidly and those that kill more slowly by retarding bacterial protein synthesis (Table 1and 2). Generally speaking, the faster-killing antibacterial agents are more desirable.

Table(1) :- Types of Antibiotics

Rapid-killing antibiotics
Penicillins and cephalosporins
Metronidazole (Flagyl®)
Fluoroquinolones
Antibiotics that slow protein synthesis
Erythromycins (macrolides)
Clindamycin (Cleocin®)
Tetracyclines

Table(2):- Common Examples of Oral Penicillins and Cephalosporins

Penicillins
Penicillin V 500 mg qid
Ampicillin 500 mg qid
Amoxicillin 500 mg tid/qid
Augmentin 500 mg tid/qid
Cephalosporins
First generation
Cephalexin (Keflex®) 500 mg qid
Cefadroxil (Duricef®) 500 mg qid
Second generation
Cefuroxime (Ceftin®) 250 or 500 mg bid
Cefaclor (Ceclor®) 500 mg tid
Third generation
Cefixime (Suprax®) 400 mg daily

Dosages may vary with the specific situation.

Fast-killing antibacterial agents are often called **bactericidal**, meaning that they are observed to kill quickly in the laboratory. **Penicillins, cephalosporins, and Metronidazole** is the bactericidal antibiotics commonly used against endodontic pathogens. The first two kill by integrating into and weakening a newly made cell wall, whereas the latter impedes DNA manufacture. Both require actively growing organisms to be effective, so antibiotics that fight bacteria by slowing their protein synthesis (bacteriostatic antibiotics) are generally not given along with these bactericidal drugs.

Allergies

Serious anaphylactic allergic reactions are rare with **oral** penicillins and cephalosporins, although they are possible. If allergic to one penicillin, the patient should

be considered allergic to all penicillins and possibly to cephalosporins as well. Because of a close molecular structure, there is about a 10% cross-reactivity between these groups, that is, 1 in 10 who are allergic to penicillins will be allergic to cephalosporins and vice versa.

Penicillins

Penicillins have a short half-life, limited to about 1 hour. It is important to tell patients the need to be prompt in taking their pills. Because they are excreted unchanged by the kidneys, they are very useful in treating urinary tract infections, where they accumulate in powerful killing levels. In patients with compromised kidney function, reducing the dosage is appropriate. The dentist should discuss with the patient's physician, if the individual patient is undergoing kidney dialysis, and tailor the penicillin or cephalosporin dosage according to the dialysis schedule.

Penicillins are unique in their lack of toxicity. That is, if the patient is not allergic, there is no maximum dose of penicillin and no side effects from over dosage.

Amoxicillin is generally considered the penicillin of first choice because of its somewhat better absorption from the gut.

Cephalosporins

Cephalosporins have been developed over the last three decades. Because of the **ß-lactam** ring, many consider them a subgroup of the penicillin family. Their improvement has seen three major improvements in their ability to kill stubborn infections, so the drugs are classed as first, second, and third generation. **First-generation cephalosporins** have the most value in dentistry since they kill most oral pathogens and should be considered for use in most infections. Second- and third generation cephalosporins are used for refractory infections, probably after laboratory results of a culture. Oral cephalosporins lag behind parenteral ones in the development process. One must give consideration to hospitalization and intravenous antibiotic therapy if the seriously ill patient does not respond to oral drug therapy.

Metronidazole

Metronidazole (Flagyl®) is also considered a bactericidal drug because of its fast killing time. It attacks the bacteria's DNA and works against obligate anaerobes but not against facultative bacteria or aerobes. **Metronidazole** is often used in combination with another antibiotic, usually **amoxicillin,** to combat the stomach ulcer–causing *Helicobacter pylori.* This combination of two fast-killing drugs also helps in severe dental infections. Periodontists find Metronidazole helpful in destroying deep-pocket anaerobes, bacteria that obviously infect the root canal in many instances. Metronidazole shares properties with disulfiram (Antabuse®), a drug used to help alcoholics avoid alcohol by inducing violent vomiting. So patients taking Metronidazole should be cautioned about not using alcohol for the time they are taking the drug plus 1 day following to allow the drug to be eliminated from their system.

The half-life of Metronidazole is in the 8- to 10-hour range. Side effects include an unpleasant, metallic taste and brown discoloration of the urine, effects that are dose related.

Macrolides

Erythromycins kill bacteria by slowing the manufacture of bacterial protein but do not alter the rate of human protein synthesis. Because of their large molecule, **erythromycins** are also called Macrolides. These drugs kill about the same bacteria as penicillins, albeit by different means, so they are the drug of choice for patients allergic to penicillins. They are notorious for causing stomach cramps because they increase gut motility, and many patients who are susceptible to this phenomenon report that they are "allergic." True allergy exists, so the doctor must use judgment based on a thorough history before deciding to use this type of drug. The Macrolides kill many gram-positive bacteria but have a limited spectrum for gram-negative bacteria. At one time, dentists were particularly fond of using erythromycins because of the lack of risk of life-threatening anaphylactic allergic reaction, but recently discovered serious interactions with other drugs have lessened their popularity. The wider-spectrum new Macrolides, **azithromycin** and **clarithromycin,** are more useful for dental infections if the practitioner is cautious of potential drug interactions. The newer Macrolides also develop higher tissue concentrations.

The half-life of most erythromycins is in the range of 1 to 2 hours, whereas the newer ones remain active longer. Clarithromycin's half-life is 6 hours, and azithromycin has a remarkable **40-hour** half-life.

Clindamycin

Clindamycin (Cleocin®) is often indicated in endodontic infections. It is rapidly and completely absorbed and has a good spectrum of killing oral pathogens, including many anaerobes. It was, however, the first antibiotic to be associated with causing pseudo membranous colitis, a life-threatening condition in which large patches of gut slough epithelium because of toxins from overgrowth of the nonsusceptible organism *Clostridium difficile*. This serious condition requires hospital management with intravenous fluids and antibiotics specific for the causative *Clostridium*. Patients being treated with Clindamycin who experience diarrhea or another gut problem should immediately be referred to their physician for evaluation. Other broad-spectrum antibiotics have been associated with this phenomenon as well.

The average half-life of Clindamycin is about 3 hours. Although Clindamycin does not cross the blood brain barrier, it does penetrate into abscesses and other areas of poor circulation rather well.

Tetracyclines

There is one standout among the tetracycline family of antibiotics: **doxycycline** (Vibramycin®). It has a long half-life and is least affected by heavy metal ions such as calcium, so the patient does not have to avoid dairy products and antacids. Tetracyclines kill the broadest spectrum of microbes of all antibiotics. They have recently found a place in periodontal infection fighting and should be included in the endodontist's armamentarium since periodontal pathogens frequently invade the root canal and periapical tissues.

Recall that all Tetracyclines cause staining of developing teeth as they bind to calcium during formation of teeth and bones. This means that their use should be avoided in children and pregnant women if at all possible.

A rare side effect is phototoxicity, where exposure to the sun causes severe sunburn or rash. Patients should be cautioned to avoid sun exposure while taking Tetracyclines unless they are sure that they are not susceptible to this side effect. Half-lives of most Tetracyclines are about 10 hours, whereas doxycycline's half-life is 16 hours, allowing twice-daily dosing.

Caveats

In prescribing antibiotics, it seems warranted to continue therapy for 2 or 3 days after symptoms have resolved. In theory, if viable bacteria are present when antibiotic levels drop below the killing threshold, mutations can occur more readily. Patients are often not conscientious about continuing medications once their symptoms resolve. A reminder telephone call to check on their condition and reinforce the need to finish their prescription is well advised.

Change in gut flora is definitely associated with increased levels of digitalis preparations, commonly used in heart conditions. Dangerously high levels can occur, and such patients need a consultation with their physician. Diminution of gut bacteria by antibiotics also changes output of vitamin K, needed in blood clotting, so patients on anticoagulant therapy should also be cautioned to consult with their physician.

Endodontists are in a unique position among dentists because of the preponderance of anaerobes in the conditions treated. A good specimen for culturing can often be obtained by needle aspiration from an abscess that has not yet drained. The specimen should be placed in an oxygen-free container available from a local hospital laboratory. A culture can be a big advantage when a patient does not respond to the first antibiotic. The practitioner can telephone the laboratory and quickly learn which drug to use next.

Hospitalization for administration of antibiotics intravenously should be considered when the patient is not responding to oral antibiotics. Many new-generation antibiotics are available only parenterally, and the continuous dosage of intravenous administration gives higher blood levels without the complication of oral dosing variables such as half-life and patient compliance. The results of culture and sensitivity tests can greatly aid in selection of the appropriate drug when hospitalization is warranted.

Use of corticosteroids to reduce inflammation remains popular among some practitioners. Reducing inflammation relieves symptoms but also reduces the efficiency of white blood cells, which are crucial to infection fighting. Sometimes prophylactic antibiotics are prescribed as a precaution when corticosteroids are used.

Antibiotic Prophylaxis

Dentists should all be aware of the need, before dental treatment, to premedicate with antibiotics patients who have certain heart ailments. Systemic diseases compromising the immune system also call for consideration of prophylactic antibiotics in situations for which they might not otherwise be indicated. The goal of **antibiotic prophylaxis** is to prevent clinical infection by helping destroy small numbers of bacteria

present before or introduced during treatment. Oral bacteria released during dental treatment clearly can cause heart and artificial joint infections. Oral streptococci, in particular, have been indicted as causative organisms for seeding heart and implanted joints, causing morbidity or even death.

PAIN CONTROL

There are three categories of pain control medications. **Narcotics** are the most powerful. They have three types of receptors in the brain. **Aspirin** and the **non steroidal anti-inflammatory drugs (NSAIDS**) make up the second category. These act at the site of injury to reduce pain-invoking prostaglandins that are made within the damaged cell. Although not classed as a pain reliever, corticosteroids relieve pain by this mechanism as well but have many side effects. Finally, **acetaminophen** (Tylenol®) is the third type. Acetaminophen acts primarily on the brain to relieve pain.

Modern endodontic therapy does not elicit much pain. However, many patients associate it with pain, partly because pain was a hallmark of early endodontic treatment and partly because the media often portray endodontics in this light. Just as a placebo will alleviate symptoms if the brain is convinced it will work, the patient who anticipates pain usually needs higher doses or stronger types of drug for relief. For patients anticipating pain, a prescription drug is often the only thing that will be effective. Surgical pain, postoperative pain, and where the patient has significant preoperative pain usually warrant narcotics.

Narcotics can cause addiction, with characteristics unique from other types of addiction. Both physical and psychological addictions occur. Patients may present a "story" of drug allergies, leaving the practitioner no choice but to prescribe narcotics. Be aware of this type of patient and make certain that there is a real medical need for narcotics; otherwise, you may be feeding someone's addiction or helping a drug pusher obtain his stock.

Morphine is available orally as Oramorph® and by other trade names. Like most other drugs given orally, because of rapid liver metabolism following oral dosing, a larger dose is required than is typical of the parenteral dose. Morphine pills are available in 10, 15, 30, 60, and 100 mg amounts. The higher levels are reserved for terminal cancer patients. For severe dental pain, such as when the bony cortical plates confine infection pressure, necessitating very strong drug therapy, morphine remains a viable choice for the astute practitioner.

Aspirin has been a standard drug for dental pain for many years and is still useful. It, however, prolongs bleeding, and for this reason is a poor presurgical drug. The anticoagulant effect comes from interference with platelet formation.

Many patients are on routine, low dosage aspirin therapy for prophylaxis against stroke or heart attack. Prior to endodontic surgery, consultation with their physician may be in order.

For patients with stomach problems, consider the use of coated aspirin, such as Ecotrin®. The coating will not dissolve until reaching the alkaline conditions of the small intestine. This means that drug action will be delayed for the usual 2-hour stomach transit time.

Non steroidal anti-inflammatory drugs (Motrin/ Advil) do not cause interruption of platelet synthesis for nearly as long because their binding to cyclooxygenase is **reversible**. Bleeding profiles return to normal shortly after NSAIDS are metabolized. Non steroidal anti-inflammatory drugs were found to be superior to 60 mg of codeine for pain relief in many pain studies.

Both NSAIDS and aspirin cause stomach upset and can be ulcerogenic. The deleterious stomach (and kidney) effects of aspirin and NSAIDS are caused by action on one of the cyclooxygenase enzymes, cyclooxygenase 1 (COX-1), which seems to predominate in the stomach and kidney.

Acetaminophen (Tylenol) gives patients relief via its action directly on an unknown site in the brain. It was discovered many years ago, and its cousin phenacetin was popularized in the now unavailable "APC" formulation of aspirin, phenacetin, and caffeine. Although it is effective against pain and fever, inflammation remains unchanged by acetaminophen. Some practitioners alternate acetaminophen and aspirin every 2 hours to enhance pain relief. Excedrin®, Goody's Headache Powder®, and other preparations contain aspirin and acetaminophen.

Acetaminophen is metabolized by the liver and should be used cautiously in patients with liver disease or chronic alcohol use. Considerable controversy exists about use of acetaminophen in alcohol abusers with compromised liver function. Most recent evidence suggests that a metabolite is the problem and that abrupt cessation of alcohol intake can lead to higher levels of the toxic metabolite than if some alcohol intake was continued. Obviously, it is best to avoid acetaminophen when liver capability is in question.

On the positive side, acetaminophen does not cause stomach irritation. Also interesting is the fact that research data show that acetaminophen is better for elevation of the threshold for sharp pain, such as with dental treatment, than other types of pain relievers.

ANXIETY REDUCTION

As mentioned earlier, many patients view endodontic therapy as a painful process and avoid treatment, to the detriment of their dental and general health. In a recent study, nearly 30% of lay persons surveyed said that they were nervous about going to the dentist. Over half of this group said that they would go to the dentist more often if given a "**sedative drug**." It is a common observation in practice that patients arrive fearful.

Benzodiazepines are now available that act directly on the brain centers that control fear. This class of drug not only relieves anxiety but is also an anticonvulsant, an amnestic, a sedative, and a muscle relaxant.

The first of the benzodiazepines discovered was **diazepam** (Valium®). Its usefulness is limited by its long half-life, approaching 60 hours. One reason for the long life span of the drug is that two of its metabolites are pharmacologically active.

Oral drug administration should occur in the office to allow monitoring and should occur about 1 hour prior to treatment. As with all CNS depressants, one must consider lowering the dose when the patient is concurrently taking another CNS

depressant. Patients must not be allowed to drive or operate machinery. Anxious patients will gladly make arrangements for a driver to escort them home.
An additional positive effect of the benzodiazepine drugs is their amnesia. Patients frequently think that the treatment took significantly less time than it actually did and also have gaps in their recall of events during the procedure, probably from a direct drug effect on their brain. Obviously, it is necessary to have a second person in the treatment