CHAPTER **40**

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INTRODUCTION

Every year, new medications are introduced into the American market, many of which are widely used by podiatrists. Although podiatrists may not prescribe all of these new medications, it is important to be aware of their existence and their use so that the podiatrist, as a healthcare provider, can provide complete care.

Four medications that have become available recently will be discussed: Actonel, Aggrenox, Avelox, and Mobic. These medications may have podiatric implications and may become useful as a form of treatment for the podiatrist. These medications were also chosen because they are ones likely to be seen given the patient population treated by podiatrists.

ACTONEL

Actonel (risedronate) is a pyridinyl biphosphonate that inhibits osteoclastic activity and modulates bone metabolism. It does this by having an affinity for hydroxyapatite crystals in bone and blocks resorption. Through this action, risedronate reduces bone turnover. Risedronate is indicated for the treatment and prevention of osteoporosis in postmenopausal women as well as glucocorticoid-induced osteoporosis. It is also indicated for the treatment of Paget's disease.

Osteoporosis is characterized by decreased bone mass and increased fracture risk, most commonly seen at the spine, hip and wrist. The diagnosis of osteoporosis can be confirmed with the findings of low bone mass, x-rays, a history of osteoporotic fractures, loss of height and by the measure of bone mineral density. Approximately 40% of 50-year-old women will experience one osteoporosis related fracture in their remaining lifetime.[1] Risedronate treatment decreases the elevated rate of bone turnover that is typically seen in postmenopausal osteoporosis.

Another cause of osteoporosis is sustained use of glucocorticoids. This form can occur in both men and women and affects all ages. In sustained glucocorticoid use, bone formation is inhibited and bone resorption is increased, leading to a net loss of bone.

Risedronate is also indicated for the treatment of Paget's disease which is a focal skeletal disorder characterized by greatly increased or disordered bone formation. This excessive osteoclastic activity is followed by osteoblastic new bone formation resulting in the replacement of normal bone architecture with disorganized, enlarged, and weakened bone structure. Risedronate is contraindicated in patients with hypocalcemia and severe kidney disease since it is cleared via the kidneys.

Podiatric Implications

In recent years, the biphosphonates have been studied as an adjunct in the treatment of patients with Charcot arthropathy in an attempt to decrease the loss of bone density during the dissolution phase. The treatment of the Charcot foot can be challenging. It includes prolonged periods of non-weightbearing, immobilization, and surgery to avoid possible amputations. Obviously, any adjunct in treatment for this disorder that can be helpful will result in a decreased morbidity.

Although the use of risedronate as treatment for Charcot arthropathy has not been published, other articles concerning such use of biphosphonates have been released.[2,3] In a paper out of France, one Charcot patient received intravenous pamidronate every four months for a period of two years. This patient, although weightbearing, did show signs of improvement.[2] In another report, involving six patients, a reduction of Charcot activity was monitored by measuring pedal temperature. A drop from 3.4 +/- 0.7 °C to 1.0 +/- 0.5 °C was reported. Also reported was a significant reduction in bone turnover as judged by a decrease in alkaline phosphate activity which fell by 25 +/- 3%.[3] This data suggests that biphosphonates may be a definitive treatment in active Charcot arthropathy.

AGGRENOX

Years ago, it was discovered that an aspirin a day helped prevent recurrent strokes or myocardial infarction in patients at risk. Since that time, other products have become available to purportedly improve on such prophylaxis. Recently, Boehringer Ingelheim has combined two older products to form a new agent in the fight against these recurrent ischemic events. Aggrenox is a combination of 200 milligrams of Dipyridamole extended release and 25 milligrams of aspirin. Aggrenox is indicated to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke secondary to thrombosis.

Mechanism of Action

Aspirin and dipyridamole both inhibit platelet aggregation, but they work by way of two different mechanisms. Aspirin irreversibly inhibits cyclooxygenase and thus inhibits the generation of thromboxane A2, a powerful inducer of platelet aggregation and vasoconstriction.[4]

Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells and erythrocytes in vitro and in vivo; the inhibition occurs in a dose-dependent manner at a therapeutic concentration (0.5 - 1.9 Fg/ml). This inhibition results in an increase in local concentrations of adenosine which acts on the platelet A2 receptor thereby stimulating platelet adenylate cyclase and increasing cAMP levels. Via this mechanism, platelet aggregation is inhibited in response to various stimuli such as collagen contact, platelet activating factor (PAF), and adenosine diphosphate (ADP).[4]

Comparison of Efficacy

The combination of aspirin and dipyridamole has shown to be effective in the prevention of recurrent strokes. There have been two large studies in Europe, the European Stroke Prevention Study I (ESPS 1) and the European Stroke Prevention Study II (ESPS 2). In ESPS 1, aspirin and dipyridamole in combination was compared to aspirin alone, Dipyridamole alone, and placebo. It was found that aspirin alone yielded a relative risk reduction score of 18.1%. Dipyridamole alone yielded a score of 16.3%, and the two combined yielded a score of 37.0%. This indicates a synergistic effect of aspirin and dipyridamole.[5] Because the relative risk reduction for stroke was increased with the combination, the survival probability was improved as well when compared to the survival probability using other regimens.[5]

In ESPS 2, the relative risk reduction score of the aspirin and Dipyridamole combination was up to 38% (average 23%). In this study, the combination was compared to other newer agents, which included clopidogrel and ticlopidine, and was shown to be more effective in the prevention of strokes.[6]

Summary

Aggrenox is dosed twice daily, one in the morning and one in the evening, without regard to meals, and has been shown to be beneficial in the fight against recurrent stroke. Although not indicated, it has potential to be used after podiatric procedures as a preventative of deep vein thrombosis in patients who are at risk. Due to its safety and efficacy, Aggrenox could be part of the podiatric pharmacological armamentarium.

AVELOX

Moxifloxacin, a new quinolone antibiotic, is marketed under the brand name Avelox by Bayer Corporation.[7] (Fig. 1) Moxifloxacin is indicated for the treatment of upper respiratory infections and is marketed as a once-a-day alternative to twice a day Ceftin™. As of this writing, it has not been marketed to podiatry, but certainly has that potential since the quinolones are a part of the treatment of lower extremity infections.

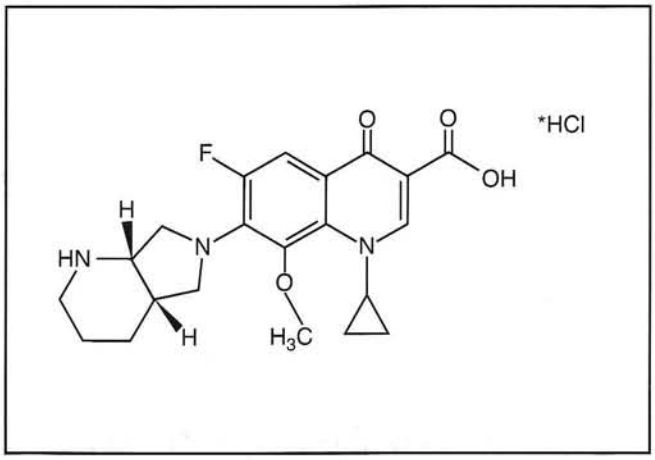

Figure 1. Chemical structure of moxifloxacin.

Indications

Moxifloxacin is indicated for upper respiratory infections, but it has been shown to be effective against the following microorganisms, some of which have been encountered in lower extremity infections.

- Aerobic Gram-positive microorganisms
  - Staphylococcus aureus (methicillin-susceptible strains only)
  - Streptococcus pneumoniae (penicillin-susceptible strains)
- Aerobic Gram-negative microorganisms
  - Haemophilus influenzae
  - Haemophilus parainfluenzae
  - Klebsiella pneumoniae
  - Moraxella catarrhalis
- Other microorganisms
  - Chlamydia pneumoniae
  - Mycoplasma pneumoniae

Safety

Avelox, dosed at 400 milligrams daily, is relatively safe, but has been shown to prolong the QT interval on EKG's in some patients. For this reason, it should not be used in patients taking certain antiarrhythmics such as quinidine, procainamide, amiodarone, or sotalol. As with other quinolones, the safety of Avelox in patients under 18 years of age has not been established and therefore should not be used.

MOBIC

Mobic (meloxicam) is the newest member of the nonsteroidal anti-inflammatory drugs (NSAIDs) to be released in the United States with reportedly decreased gastrointestinal side effects. Meloxicam is not classified as a COX-2 specific NSAID because the percentage of COX-2 inhibition is less than the FDA guidelines. However, it does possess decreased inhibition of the COX-1 receptors and this allows it to potentiate less gastrointestinal disturbances than other NSAIDs.

Meloxicam is available in 7.5 and 15 milligram tablets and is dosed once daily. It takes 3 to 5 days to reach steady state so patients should be instructed that they might not feel an improvement until that time.

Since the benefits of COX-2 specific NSAIDs are well known at this point, Table 1 will compare the differences in these new agents.[8-10] It presents a comparison of the three newest NSAIDs, Mobic (meloxicam), Celebrex (celecoxib), and Vioxx (rofecoxib). These new NSAIDs, with less COX-1 inhibition, have an advantage over the other NSAIDs, in that there is a decreased incidence of GI upset, which is of benefit in our aging population.

Table 1

Comparison of Meloxicam, Celecoxib and Refecoxib

	Meloxicam (Mobic®)	Celecoxib (Celebrex®)	Rofecoxib (Vioxx®)
Mechanism of action	Inhibits COX-1 & COX-2	Inhibits COX-2	Inhibits COX-2
Pharmaco-kinetics	Hepatically metabolized Excreted in urine/feces	Hepatically metabolized Excreted in urine/feces	Hepatically metabolized Excreted in urine/feces
Dosage adjustments	Elderly females but not in mild renal failure	Renal impairment but not in elderly	Renal impairment but not in elderly
GI studies	Decreased incidence of ulcers compared to other NSAIDs	Decreased incidence of ulcers compared to other NSAIDs	Decreased incidence of ulcers compared to other NSAIDs
Platelet effects	Increased bleeding time	No effect on bleeding time	No effect on bleeding time
Drug interactions	ACE Inhibitors Lasix Lithium High dose ASA Low Dose ASA	ACE Inhibitors Lasix Lithium High dose ASA	ACE Inhibitors Lasix Lithium High dose ASA Methotrexate Coumadin
Indications	Osteoarthritis	Osteoarthritis Rheumatoid arthritis	Osteoarthritis Acute pain Dysmenorrhea
Dosage	7.5-15 mg QD - Osteoarthritis	200 mg QD - Osteoarthritis 200 mg BID - Rheumatoid Arthritis	12.5-25 mg QD - Osteoarthritis 50 mg QD - pain
Advantages	No dosage adjustment necessary in mild/ moderate renal disease	Safer in PUD patients No need to DC preop	Safer in PUD patients No need to DC preop Has pain indication
Disadvantages	Not COX-2 specific	Allergy to Sulfonamides	Fluid retention

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