MEDICATIONS USED IN THE RHEUMATIC DISEASES

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While this is intended to be an "all encompassing" review of medications used in the treatment of rheumatic diseases, the very nature of anything alleging to be "all encompassing" is such that it is doomed to fail. Hopefully, any shortcomings in this paper will be of minimal import relative to the need for such information by the podiatrist.

NSAIDS

The most well known and frequently used preparations in the treatment of rheumatic disease are the non-steroidal anti-inflammatory drugs (NSAIDs). They are a diverse group of mostly acidic compounds that have revolutionized the treatment of the arthropathies over the past 100 years. In the past 25 years, the availability of these compounds has grown explosively and as a group they are probably the most widely used (prescribed and over the counter) medications in the world.

As a class, the NSAIDs exert their action by inhibiting the production of various prostaglandins which are the body's chemical mediators of inflammation. This inhibition is accomplished primarily by suppressing cyclooxygenase, an enzyme responsible for the metabolic cascade of arachidonic acid to endoperoxides and subsequently to prostaglandins (Figure 1).

NSAIDs are potent suppressors of inflammation but with the exception of scattered anecdotal reports of certain compounds, they do not affect the course of any of the diseases in which they are used. They frequently relieve pain, swelling and other manifestations of inflammation but have no effect on the progression or the destruction that may be a part of some diseases. Despite that significant limitation, NSAIDs are extremely useful and have improved the quality of life for millions of arthritic patients.

DRUG INTERACTION OF NSAIDS

The NSAIDs are generally albumin-bound and so may competitively seek binding sites with other albumin-bound drugs. The most notable examples of such drug-drug interference are with the oral anticoagulants (e.g., Coumadin) and with the oral anti-diabetic agents (sulfonylureas). The combination of such medications may cause displacement by one or the other (or both) from its binding site on albumin. This increases the "free" drug (unbound drug) blood levels which will increase the effect of that particular agent beyond what may be expected for the dose utilized. This

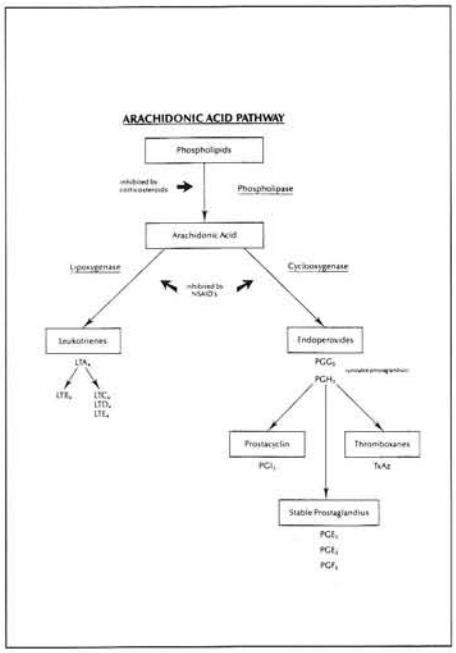

Fig. 1. Arachidonic Acid Pathway

is a problem when starting, stopping or changing the dose of any of the drugs, as that often causes expected levels and actual levels to vary.

TOXICITY OF NSAIDS

Toxicity of the NSAIDs is real. While the side effects of associated morbidity and mortality are of great concern, judicious use of these agents has permitted a better way of life for millions of patients with a real but acceptable toxicity profile. The most frequent and well known side effects are those exerted on the gastro-intestinal (GI) tract. Because of suppression of prostaglandins (PG's) there is good news and bad news. The good news is that adequate suppression of PG's improves the symptoms of the arthropathy. The bad news is that GI tract integrity is dependent on the presence of certain PG's. Suppression of those PG's leaves the stomach mucosa open to irritation, erosion, ulcer and bleeding. This effect is not totally local since it has been demonstrated that circulating NSAIDs can enter the cells of the GI tract from the circulation and exert their toxic (and good) effects in that manner (the so-called "back door" approach). From a practical standpoint, this means that NSAIDs given by suppository, intravenously, intramuscularly, sublingually or by any other route that may bypass direct contact with stomach mucosa may still exert GI effects, though usually to a lesser degree.

The NSAIDs also may exert effects on the liver, the kidney or the bone marrow. While these are less common than the GI effects, they are certainly not unheard of and the prescribing physician must be vigilant for their presence. There are also unusual problems that may occur such as the rare aseptic meningitis that may be associated with ibuprofen in lupus patients. These side-effects are uncommon enough that one has to have heard of them before one can even consider their presence.

DECREASED PLATELET FUNCTION (NSAIDS)

The well described and frequently stated decreased platelet adhesiveness associated with NSAIDs is of concern to surgeons in particular. While it is often discussed, it is important to realize that it is more of a theoretical than real problem. Bleeding associated with decreased platelet adhesiveness (but not necessarily bleeding associated with thrombocytopenia from NSAID induced marrow suppression) is extremely rare. Also, the effects of aspirin (or other acetylated salicylates) of platelet adhesiveness is different from all the other NSAIDs. Aspirin's effect on platelets is irreversible; therefore any platelet exposed to aspirin loses its "stickiness" and removal of the aspirin does not reverse that. The life of a platelet is approximately ten days with roughly one-tenth of all platelets "dying" and one-tenth "being born" every day. This is the rationale for low dose (one every other day) aspirin use in preventing heart attack and stroke. The surgeon may want to consider discontinuing aspirin as many as five to ten days before an elective procedure to avoid any potential hemostatic problems, though the rarity of any such problems should offer some solace to the surgeon faced with an emergent/non-elective procedure. The other NSAIDs exert their effects on platelet adhesiveness in a reversible manner. Removal of the offending NSAID allows the platelet to revert to its "normal" state.

The practical significance is that the concern over the hemostatic problems is lessened and the surgeon need merely look up the half-life of the particular compound and request that the patient discontinue it about three to five half-lives before the procedure is scheduled. That time will obviously be shorter for drugs such as tolmetin and fenoprofen than it will for naproxen and piroxicam. Again, one usually proceeds in the emergent situation fairly safe in the knowledge that actual hemostatic problems are rare.

Finally, most of the drugs are active agents while others are pro-drugs (i.e., the active compound is a metabolite of the ingested compound). Some seem to have more GI toxicity than others, some seem to have more renal effects than others and some seem to have more hepatic effects than others. If one has a choice it is best to tailor the known effects (good and bad) to the individual's situation as much as possible. However, this remains tempered by the fact that much toxicity is idiosyncratic and unpredictable and the same can be said for efficacy in any particular individual.

OTHER ANTI-RHEUMATIC DRUGS

While the NSAIDs are extremely useful, relatively safe and most often "first line" agents, there are many other drugs used in the treatment of rheumatic diseases. The concept of "first line" versus "second line" drugs is changing. More recent opinions (as yet unproved) are suggesting that many of the "second line" agents should possibly be used earlier in the treatment of systemic inflammatory diseases such as rheumatoid in hopes of obtaining better results. Without discussing that debate, this article will refer to these drugs as "second line" agents keeping in mind the differences of opinion. This group of drugs has been referred to as "remittive agents," disease-modifying anti-rheumatic drugs (DMARD's), slow-acting anti-rheumatic drugs (SAARD's) and second line agents. None of the names are totally true or totally appropriate — thus the multiplicity of names. They will be called DMARD's for purposes of this discussion.

Some of the effects of the DMARD's used in the treatment of rheumatic diseases were discovered serendipitously while others were the result of careful and deliberate study. Some are related to each other and many are totally unrelated except for their use in the same disease. More are used in rheumatoid arthritis than in the other systemic inflammatory diseases but at least part of this fact is that rheumatoid arthritis is the most common of such diseases, therefore, there are more patients to study.

HYDROXYCHLOROQUINE (PLAQUENIL)

Hydroxychloroquine (Plaquenil) is an antimalarial agent approved for use in both rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It is an oral agent, has a somewhat bitter taste (as all quinine derivatives do) and has a duration of onset of about two to four months. It appears to have its best effects in earlier/milder rheumatoid and more recently has been studied in combination with other DMARD's in more aggressive disease. SLE patients that have rashes are more likely to benefit from hydroxychloroquine. It has relatively few side effects (skin, marrow, central nervous system, retinal toxicity)) with the most feared being that of retinal toxicity. Patients should have ophthalmologic evaluation prior to its use and every six months while taking it. The retinal damage may be irreversible and seems related more to a higher daily dose than to the overall duration of therapy. Another antimalarial agent, chloroquine (Aralen), is also approved for use although some say it has a slightly greater potential for retinal toxicity and so is used less frequently. The usual daily dose of hydroxychloroquine is 200 milligrams twice a day. The average cost to the patient will be about sixty dollars per month.

GOLD PREPARATIONS

Gold preparations have been used for more than 50 years in rheumatoid arthritis and have repeatedly been shown to be of value. It is available by injection as gold sodium thiomalate (GST, Myochrysine) or as aurothioglucose (AIG, Solganol). In the last 10 years, an oral preparation, auranofin (Ridaura), has been available. There appears to be more toxicity with the injectable agents but they also possess greater efficacy than the oral agent. Duration of onset of effect is at least three to six months, possibly longer. GST and ATG are given weekly at about 50 milligrams per week after one or two weeks of lower "test" doses. When some measure of efficacy is achieved, which may be up to 20 weeks, dosage is lowered by increasing duration between injections to two weeks and then to three weeks and eventually four weeks. Side effects include rash, itching with or without rash, mouth sores, a "funny" taste sensation, marrow suppression or toxicity, renal damage and more rarely lung or colon involvement. GST may be associated with nitritoid reaction as well. This is manifested by flushing, anxiety, nausea, and weakness within an hour of the injection. Its severity and frequency decreases with continued use. Auranofin may be associated fairly frequently with diarrhea, while that is not the case with injectable types of gold. Gold must be monitored at each injection by obtaining complete blood count (CBC) and urinalysis (U/A) although some physicians obtain those studies every other time. Costs are difficult to estimate since the costs of an office visit, injection and laboratory studies all play a role. However, the cost of oral gold (not including monitoring) is approximately sixty dollars per month. The cost of injectable gold will usually be greater than that when taken weekly and significantly

less than that when injections can be given monthly. Gold is approved in RA but is used by many physicians in other diseases as well (psoriatic arthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis).

D-PENICILLAMINE

Another agent used in RA and other conditions is d-penicillamine (Cuprimine, Depen). Its efficacy and toxicity are similar to gold, though the side effects seem to occur more frequently. Other medications have to some degree seemed to supplant it in recent years. It is still useful but there are some unusual side effects that have occurred (pemphigus, myasthenia gravis, Goodpasture's Syndrome, lupus-like illness, cholestatic jaundice, a fatal bronchiolitis and others). While these side effects are rare, they have occurred often enough to limit the drugs usefulness. The drug is taken by mouth, usually beginning with 125 to 250 milligrams per day and slowly increasing the dose over months. The eventual usual dose is 500 to 750 milligrams per day at a cost of sixty to ninety dollars to the patient per month in addition to the cost of monitoring laboratory studies. Its duration to efficacy is two to four months and it is best taken on an empty stomach because food decreases its absorption.

METHOTREXATE

Methotrexate (Rheumatrex and generic) is one of the most significant "rediscoveries" of the last ten years or so. A folic acid antagonist — available and used for malignancies since the early 1950s - methotrexate (MTX) was used successfully in the 1950s for various rheumatic conditions, most notably RA. However, its toxicity profile was rather high and use was "put on the back burner" for the next twenty years, though not totally abandoned. In the late 1970s to early 1980s it became apparent that dosage could be drastically cut when compared to anti-cancer dosages at little or no sacrifice in efficacy. This has led to its widespread use in the last decade with quite minimal toxicity.

The drug is taken once a week in either divided doses over a 12 to 24 hour period or as a single dose. The oral route appears to be as effective as the intramuscular route. The usual dose is seven and one-half to fifteen milligrams per week with few patients requiring either higher or lower doses, and an effect can usually be appreciated in four to eight weeks.

The concomitant use of daily folic acid seems to decrease overall side effects and intramuscular use may decrease any gastrointestinal side effects. Adverse effects include anorexia, nausea, mouth sores (the most common side effect), marrow suppression, hepatic toxicity and, rarely, hepatic fibrosis (cirrhosis). A rare but severe allergic pneumonitis may occur and infections such as herpes zoster and Pneumocystis carinii may be more common in those taking MTX. Agents containing sulfa (including trimethoprim sulfamethoxazole and sulfasalazine) may increase the suppressant effects of MTX and liver toxicity is more frequent in those with a history of hepatitis, chronic ethanol use and abuse, and insulin-dependent diabetes mellitus. Blood counts and liver function studies should be done monthly to monitor for toxicity and renal function studies can be done less often. There is a debate as to whether and how often liver biopsies should be performed, but the manufacturer still recommends doing so at approximately every 1500 milligrams. Renal insufficiency increases the potential for toxicity, and the concomitant use of NSAIDs may also increase MTX toxicity. Despite all of the previously mentioned effects, MTX appears to be gaining favor as a first line DMARD and toxicity is not particularly common. MTX costs approximately forty to eighty dollars per month, plus the cost of monitoring.

AZATHIOPRINE (IMURAN)

Another of the anti-cancer drugs, azathioprine (Imuran) has a well-known place in the treatment of rheumatoid arthritis, systemic Lupus and other inflammatory connective tissue diseases. It is a perinea analog immunosuppressive agent that appears to be about as effective as gold and penicillamine, though one study suggests that radiologic evidence of erosions in RA may progress more rapidly with azathioprine than with MTX. This has yet to be proven. Toxicity is increased with concurrent use of allopurinol (Zyloprim) since it may interfere with azathioprine's metabolism. There also is a low but definite increased incidence of malignancy after years

of use of azathioprine - the most likely ones being leukemia and lymphomas — and more common side effects include gastrointestinal symptoms, hepatitis and bone marrow suppression.

SULFASALAZINE (AZULFIDINE)

Sulfasalazine (Azulfidine) has been used for years in inflammatory bowel disease and was used years ago for rheumatoid arthritis. It has recently again found favor in the treatment of RA, particularly since its effect appears to be close to that of gold or penicillamine but with less toxicity. Disturbances of the GI tract and rashes are relatively common while hepatotoxicity and marrow suppression though fairly rare, are possible.

CYTOTOXIC/IMMUNOSUPPRESSIVE DRUGS

Other cytotoxic/immunosuppressive drugs are used in many of the rheumatic diseases to a lesser degree than those described above primarily because of either less efficacy, greater toxicity or other considerations. These include cyclophosphamide (Cytoxan), chlorambucil (Leukeran) and others. It is of particular note to be aware of the markedly increased survival and decreased morbidity when cyclophosphamide is used in certain patients with lupus nephritis or Wegener's Granulomatosis. Its use has revolutionized treatment of those conditions.

CORTICOSTEROIDS

No discussion of the rheumatic diseases is complete without at least touching upon the use of steroids — a topic in and of itself long enough to fill volumes. The corticosteroids are one of the most valuable medical discoveries of the 20th century (for any and all inflammatory diseases, not just rheumatic conditions) and, at the same time, among the most toxic. In most diseases, the potential toxicity lies in the ability to suppress inflammation profoundly, while at the same time having nothing more than a "masking" effect on the underlying disease. However, in many diseases (lupus nephritis, polymyositis, polymyalgia rheumatica and others), corticosteroids have unquestionably vastly improved the quality of life while at the same time greatly prolonging life as well. The scope of this paper does not permit an in-depth discussion of uses, and doses, but generally the lowest dose possible should always be used. Remember that when starting steroids, an end-point should always be in mind.

SUMMARY

As with any family of diseases, the rheumatic diseases are ineffectively and inefficiently treated so research continues. At this point in time, much of the exciting research is being done along the lines of immunomodulation/immunoregulation and is being aimed at the immune system in general (cyclosporine, the interleukens, etc.) or specific defects (anti-CD4 monoclonal antibodies, etc.) These studies are in their early phases, however. Immunomodulators such as the anti-helminthic agent levamisole have been used for years with varying success and are being restudied. Combinations of drugs are being studied with variable levels of success and failure as well.

This review should give the reader some insight into the breadth and depth of the drugs used in rheumatic diseases, the potential toxicities and the expense of such treatment. The latter includes such "hidden" costs as time off from work to receive therapy (e.g., gold shots), laboratory monitoring for toxicity (e.g., gold, MTX, d-penicillamine, azathioprine, etc.), and consulting physician expenses for monitoring some drugs (ophthalmologic evaluation for hydroxychloroquine use, liver biopsy for MTX use). While many of these drugs have had a major impact on morbidity and mortality in these diseases, there is obviously still a long way to go.

Bibliography

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