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DRUGS OF CHOICE FROM THE MEDICAL LETTER

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CONTENTS

DRUGS FOR RHEUMATOID ARTHRITIS

Many different drugs are now used to treat rheumatoid arthritis. Nonsteroidal anti-inflammatory drugs (NSAIDs), listed in the table on page 16, have analgesic and anti-inflammatory effects, but may not affect the disease process. The "disease-modifying" antirheumatic drugs (DMARDs) listed on page 18 have no immediate analgesic effects, but can control symptoms and may delay progression of the disease. Interactions of anti-rheumatic drugs with other drugs are listed in *The Medical Letter Handbook of Adverse Drug Interactions*, 2001.

NSAIDS — No NSAID is consistently more effective than any other, but some patients who do not respond to or tolerate one drug may respond to or tolerate another. Aspirin in high doses is as effective as any other NSAID, but may have more gastrointestinal toxicity.

Mechanism of Action — The anti-inflammatory effect of NSAIDs is due mainly to inhibition of the two isoforms of cyclooxygenase, COX-1 and COX-2. COX-1 is expressed in most tissues and is thought to protect the gastric mucosa. COX-2 is expressed in the kidney and brain and its expression can be induced in the ovary, uterus, cartilage and bone, and at sites of inflammation. Inhibition of COX-1 decreases synthesis of thromboxane in platelets and interferes with their aggregation. Inhibition of COX-2 decreases synthesis of prostacyclin in endothelium and may have a prothrombotic effect (BF McAdam et al, Proc Natl Acad Sci USA 1999; 96:272). Older NSAIDs, in varying degrees, block both COX isoforms. Celecoxib (*Celebrex* – Medical Letter 1999; 41:11) and rofecoxib (*Vioxx* – Medical Letter 1999; 41:59) in therapeutic doses selectively inhibit COX-2 but not COX-1.

Gastrointestinal Adverse Effects – All NSAIDs can cause dyspepsia and more serious gastrointestinal (GI) toxicity, including gastric and duodenal ulceration, perforation and bleeding, with or

without warning symptoms in any age group, but especially among elderly patients. Meclofenamate may cause a high incidence of diarrhea. Piroxicam, which has a longer half-life, should be avoided in elderly patients. Concurrent use of misoprostol *(Cytotec)*, a prostaglandin analog, or possibly a histamine H_2-receptor antagonist such as famotidine *(Pepcid)* in high doses or a proton pump inhibitor such as omeprazole *(Prilosec)*, may decrease the incidence of GI toxicity caused by NSAIDs (P Schoenfeld et al, Aliment Pharmacol Ther 1999; 13:1273).

Celecoxib and rofecoxib have less upper GI toxicity than older, less selective NSAIDs, at least in the short term (one year or less) in patients not taking aspirin for cardiovascular prophylaxis (DR Lichtenstein and MM Wolfe, JAMA 2000; 284:1297). In a randomized, double-blind trial in almost 8000 patients with osteoarthritis or rheumatoid arthritis, celecoxib 400 mg b.i.d. (higher than recommended for any indication) was associated with fewer symptomatic ulcers or upper GI complications than ibuprofen 800 mg t.i.d. or diclofenac 75 mg b.i.d. In patients also taking aspirin, however, the incidence of GI toxicity was similar with either celecoxib or the older NSAIDs (FR Silverstein et al, JAMA 2000; 284:1247). With rofecoxib 50 mg daily, 2.1 confirmed GI events occurred per 100 patient-years, compared to 4.5 with naproxen 500 mg b.i.d. (C Bombardier et al, N Engl J Med 2000; 343:1520). Whether serious GI bleeding will occur less frequently with long-term use of celecoxib and rofecoxib than with older NSAIDs remains to be established, particularly in patients also taking cardioprotective doses of aspirin.

Effects on Bleeding and Myocardial Infarction – With the exception of nonacetylated salicylates, the selective COX-2 inhibitors and possibly meloxicam and nabumetone, all NSAIDs can interfere with platelet function and prolong bleeding time. This effect is reversible when the drug is cleared, except with aspirin. Use of selective COX-2 inhibitors, which do not interfere with platelet function and decrease the antithrombotic effect of endothelial prostacyclin, could have a prothrombotic effect leading to a higher incidence of cardiovascular events. The higher incidence of myocardial infarction in some studies of patients taking celecoxib or

rofecoxib (and not taking aspirin) could also be due to the loss of a cardioprotective effect provided by a non-selective NSAID. Whether myocardial infarction will occur more frequently with long-term use of celecoxib and rofecoxib than with older NSAIDs remains to be established.

Renal Toxicity – Due to inhibition of renal prostaglandins, all NSAIDs, including selective COX-2 inhibitors, decrease renal blood flow, cause fluid retention and may cause renal failure in some patients, particularly the elderly (SK Swan et al, Ann Intern Med 2000; 113:1). Diminished renal function or decreased effective intravascular volume due to diuretic therapy, cirrhosis or congestive heart failure increases the risk of NSAID renal toxicity.

CNS Toxicity – All NSAIDs can cause central-nervous-system (CNS) effects such as dizziness, anxiety, drowsiness and confusion. Indomethacin (*Indocin*, and others) may cause more severe CNS adverse effects than other NSAIDs and should be used cautiously in the elderly; depression, disorientation and, especially, severe headache occur frequently with higher doses. Tinnitus has been associated particularly with high doses of salicylates. Aseptic meningitis has occurred rarely in patients with systemic lupus erythematosus or other connective tissue diseases taking ibuprofen, tolmetin or sulindac and has been reported with ibuprofen and naproxen in patients without any connective tissue disease.

Hepatic and Other Toxicity – NSAIDs frequently cause small increases in aminotransferase activity; serious hepatic toxicity is rare, but occurs more frequently with diclofenac. Pancreatitis also has been reported. Cholestatic hepatitis has been reported with celecoxib, which is a sulfonamide (MV Galan et al, Ann Intern Med 2001; 134:254).

NSAIDs rarely cause blood dyscrasias; aplastic anemia has been reported with ibuprofen, fenoprofen, naproxen, indomethacin, tolmetin and piroxicam. Asthmatic patients sensitive to aspirin could develop severe bronchospasm and anaphylactoid reactions with any NSAID; nonacetylated salicylates are less likely to cause reactions in these patients, and one report suggests that selective

COX-2 inhibitors may also be less likely to do so (B Dahlén et al, N Engl J Med 2001; 344:142). Various types of dermatological toxicity have been reported with NSAIDs, including photosensitivity and toxic epidermal necrolysis. Celecoxib is contraindicated in patients allergic to sulfonamides. Use of NSAIDs by pregnant women has been associated with persistent pulmonary hypertension in their offspring (MA Alano et al, Pediatrics 2001; 107:519).

Drug Interactions – NSAIDs may interact with many drugs; they may, for example, decrease the effectiveness of diuretics, beta-blockers, ACE inhibitors and some other antihypertensive drugs, and may increase the toxicity of lithium and methotrexate (*The Medical Letter Handbook of Adverse Drug Interactions*, 2001, page 371). Celecoxib and rofecoxib can increase INR and the risk of bleeding if given with warfarin (*Coumadin*, and others); the effect is unlikely to be clinically significant, but patients should be monitored for INR changes (*The Medical Letter Handbook of Adverse Drug Interactions*, 2001, page 64).

DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs) — Most clinicians begin therapy with a DMARD—often hydroxychloroquine or sulfasalazine for mild rheumatoid arthritis or methotrexate if the disease is more severe—in addition to an NSAID at the time of diagnosis. Most DMARDs have a slow onset of action and require regular monitoring for adverse effects.

HYDROXYCHLOROQUINE (*Plaquenil*, and others) — The antimalarial hydroxychloroquine, 200 mg twice daily, is moderately effective for mild rheumatoid arthritis and is usually well tolerated (JD Jessop et al, Br J Rheumatol 1998; 37:992). The drug's effectiveness may require three to six months to become apparent. Nausea and epigastric pain can occur, but serious adverse effects are rare. Hemolysis may occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Retinal damage has been reported, but can be avoided if vision is monitored (visual fields, color vision) at six- to twelve-month intervals, dosage is kept below 6.5 mg/kg/d, and the drug is discontinued promptly when signs of retinal toxicity first appear (GD Levy et al, Arthritis Rheum 1997; 40:1482; JA Block, Lancet 1998; 351:771).

METHOTREXATE (*Rheumatrex*, and others) — Oral methotrexate in low dosage decreases symptoms, improves the long-term outcome of rheumatoid arthritis, and is often used initially. Medical Letter consultants recommend starting with 7.5 mg once a week taken as a single dose or over 24 hours, which can be increased gradually to 15 to 25 mg once a week. The anti-rheumatic effect of low-dosage once-weekly methotrexate is often apparent within four to six weeks. Intramuscular or subcutaneous methotrexate once weekly may be helpful for patients who have adverse GI effects or lose benefit over time with oral dosage. Folic acid supplements of 1 to 4 mg per day are recommended (SL Morgan et al, BioDrugs 1997; 8:164).

Adverse Effects — In low dosage, methotrexate is often well tolerated, but may cause stomatitis, anorexia, nausea, abdominal cramps and increased aminotransferase activity, and rarely bone marrow suppression, pulmonary toxicity and hepatic fibrosis. Anorexia, nausea and vomiting are less frequent with parenteral use of the drug. Hypersensitivity pneumonitis, which can be severe, occurs in 1% to 4% of rheumatoid arthritis patients taking methotrexate and may be more common in patients with antecedent lung disease. Cutaneous necrotizing vasculitis has been reported rarely (TH Simonart et al, Clin Rheumatol 1997; 16:623). The drug is immunosuppressive; infections such as herpes zoster and *Pneumocystis carinii* have been reported to be more common in patients taking methotrexate for rheumatoid arthritis. An association has been reported between methotrexate and lymphoma, but spontaneous remission has occurred in some patients with discontinuation of the drug; cause and effect remain to be established (L Georgescu and SA Paget, Drug Saf 1999; 20:475). Most clinicians would not prescribe methotrexate for patients with pre-existing liver disease or significant alcohol use. Since the drug is eliminated primarily by renal excretion, serious toxicity is more likely in patients with diminished renal function.

Methotrexate is teratogenic and should not be given to women who are or may become pregnant. It is also an abortifacient and can decrease fertility in both men and women. Men should not take the drug, if possible, for at least three months before a

planned conception. Women should not take the drug for one menstrual cycle before planned conception.

In elderly patients or others with decreased renal function, concurrent use of an NSAID, which is common, increases serum concentrations and the toxicity of methotrexate (*Medical Letter Handbook of Adverse Drug Interactions*, 2001, page 339). The risk of elevated aminotransferase activity is increased in patients taking methotrexate concurrently with leflunomide; serious liver disease has been reported (ME Weinblatt et al, Arthritis Rheum 2000; 43:2609). Trimethoprim/sulfamethoxazole (*Bactrim*, and others), trimethoprim (*Proloprim*, and others) and possibly sulfasalazine may increase bone marrow suppression due to methotrexate (A Steuer and JM Gumpel, Br J Rheumatol 1998; 37:105).

SULFASALAZINE (*Azulfidine*, and others) — Sulfasalazine is also effective for treatment of rheumatoid arthritis, but has greater toxicity than hydroxychloroquine (ME Weinblatt et al, J Rheumatol 1999; 26:2123). The usual dosage of sulfasalazine is 2 g/day. Most clinicians begin with lower doses and increase gradually to minimize adverse effects. Some clinicians increase the dose to 3 grams per day if necessary.

Adverse Effects — Nausea, anorexia and rash are fairly common with sulfasalazine. Serious reactions such as hepatitis and blood dyscrasias are rare and usually occur within the first two to three months of treatment. A lupus-like syndrome has been reported. Sperm counts may decrease, but return to normal after withdrawal of the drug. Use of enteric-coated sulfasalazine (*Azulfidine En-tabs*, and others) decreases GI toxicity. Hemolysis may occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

GOLD — Gold salts have been used for many years for treatment of severe rheumatoid arthritis and sometimes can induce a complete remission. Gold sodium thiomalate *(Aurolate)* and aurothioglucose *(Solganal)* are two injectable preparations available in the USA. An oral preparation, auranofin *(Ridaura)*, is also available; it is less effective than injectable gold.

Dosage – The usual dosage of injectable gold includes a test dose of 10 mg, followed one week later by 25 mg once a week for one or two weeks, and then 50 mg weekly for up to 20 weeks, or sometimes longer if improvement continues. Response usually occurs within three to six months after starting treatment. If a response occurs, treatment intervals may be increased to every two weeks, then every three weeks, and then monthly. Most patients who respond should remain on monthly therapy; some patients may require shorter intervals. Discontinuing maintenance gold therapy may result in recurrence of arthritis that may not remit when gold is re-instituted. The dosage of auranofin is 3 mg twice a day or 6 mg once daily. If the disease does not respond within three to six months, dosage may be increased to 3 mg t.i.d. if tolerated. If the response is still unsatisfactory, the drug should be discontinued.

Adverse Effects – Many patients discontinue injectable gold because of adverse effects, particularly stomatitis, rash, proteinuria and, less commonly, leukopenia and thrombocytopenia. A complete blood count and urinalysis is recommended before each dose to detect drug-related cytopenia or proteinuria. Pruritic rash and stomatitis sometimes resolve if therapy is withheld for a few weeks and then re-started cautiously at a lower dose. Enterocolitis and aplastic anemia are rare but potentially fatal adverse effects. Interstitial pneumonitis is another rare but serious adverse effect. Gold thiomalate uncommonly causes a "nitritoid" reaction, which can be severe, characterized by flushing, weakness, nausea and dizziness within 30 minutes of injection. These reactions rarely occur with aurothioglucose. Oral gold causes less mucocutaneous, bone marrow and renal toxicity than injectable gold, but more diarrhea and other GI reactions. Gold therapy is not recommended for use during pregnancy.

LEFLUNOMIDE *(Arava)* — An oral pyrimidine synthesis inhibitor (Medical Letter 1998; 40:110), leflunomide in 6- to 12-month clinical trials was as effective as methotrexate or sulfasalazine in decreasing signs and symptoms and slowing radiologic progression of rheumatoid arthritis (JS Smolen et al, Lancet 1999; 353:259; V Strand et al, Arch Intern Med 1999; 159:2542; JT Sharp et al,

Arthritis Rheum 2000; 43:495). Long-term data are not available. After a loading dose of 100 mg daily for three days, the maintenance dose is 20 mg daily; if not well tolerated, it can be reduced to 10 mg daily.

Adverse Effects – Diarrhea occurs frequently. Reversible alopecia, rash and increases in aminotransferase activity can occur, and patients should be monitored for hepatic toxicity. Anaphylaxis, Stevens-Johnson syndrome and leucocytoclastic vasculitis have been reported. Leflunomide is carcinogenic and teratogenic in animals and contraindicated during pregnancy. Women who want to become pregnant and men who want to father a child after beginning treatment with the drug should first discontinue it and take cholestyramine (*Questran*, and others) 8 grams t.i.d. for 11 days to bind and eliminate the drug; women should then verify that plasma levels of the metabolite are <0.02 mg/L. Without cholestyramine, it could take up to two years for serum concentrations of the drug to become undetectable. The active metabolite of leflunomide inhibits CYP2C9 and can lead to increases in serum concentrations of many drugs, including some NSAIDs. Combining leflunomide with methotrexate increases the risk of elevated aminotransferase activity.

AZATHIOPRINE *(Imuran*, and others) — Azathioprine, a purine analog immunosuppressive drug, given in a dosage of 1 to 2.5 mg/kg/day can also be effective for refractory rheumatoid arthritis, but some patients cannot tolerate it (CR Yates et al, Ann Intern Med 1997; 126:608; K Gaffney and DGI Scott, Br J Rheumatol 1998; 37:824).

Adverse Effects — Nausea, vomiting, abdominal pain, hepatitis and reversible bone marrow depression can occur with azathioprine. An increased risk of lymphoma has been reported. Concurrent use of allopurinol (*Zyloprim*, and others) seriously increases azathioprine toxicity and dosage adjustment is necessary (*Medical Letter Handbook of Adverse Drug Interactions*, 2001 page 25). Azathioprine is not recommended for use during pregnancy.

TUMOR NECROSIS FACTOR (TNF) INHIBITORS — Two injectable drugs that bind to and block the activity of TNF are also used

to treat rheumatoid arthritis (Medical Letter 1998; 40:110; DA Fox, Arch Intern Med 2000; 160:437). TNF, a cytokine that causes inflammation, is present in the synovium and leads to recruitment of inflammatory cells, neoangiogenesis and joint destruction (EHS Choy and GS Panayi, N Engl J Med 2001; 344:907). **Etanercept** *(Enbrel)*, given subcutaneously, is a recombinant version of the soluble human TNF receptor. **Infliximab** *(Remicade)*, given intravenously, is a chimeric human/mouse anti-TNF monoclonal antibody (Medical Letter 1999; 41:19; B Jarvis and D Faulds, Drugs 1999; 57:945).

In patients who had failed to respond adequately to methotrexate alone, addition of **etanercept**, 25 mg twice a week for four months, was more effective than placebo in improving signs and symptoms of rheumatoid arthritis (ME Weinblatt et al, N Engl J Med 1999; 340:253). In patients with early rheumatoid arthritis, etanercept alone was more effective than methotrexate in decreasing symptoms and slowing joint damage (JM Bathon et al, N Engl J Med 2000; 343:1586). In patients with persistently active rheumatoid arthritis **infliximab** added to methotrexate in doses of 3 or 10 mg/kg IV at four- to eight-week intervals improved symptoms and stopped progression of joint damage (PE Lipsky et al, N Engl J Med 2000; 343:1594).

Adverse Effects – Injection-site reactions are common with **etanercept**, and auto-antibodies were detectable in some patients. Demyelinating disorders, including multiple sclerosis, myelitis and optic neuritis, have been associated with use of etanercept, but cause and effect has not been established. Fatal pancytopenia has occurred rarely. Adverse effects of **infliximab** include headache, infection and infusion reactions associated with administration of the drug (fever, urticaria, dyspnea and hypotension). Some patients developed anti-infliximab or auto-antibodies, and a few patients developed anti-nuclear antibodies and a lupus-like syndrome. Combined use with immunosuppressants may decrease development of anti-infliximab antibodies. Whether long-term use of TNF inhibitors such as etanercept or infliximab could increase the incidence of other auto-immune diseases is unknown. Serious infections, including tuberculosis and sepsis, have been reported with

both etanercept and infliximab; they should not be given to patients with active localized or chronic infections. Lymphoma and other malignancies have been reported in association with both drugs, but cause and effect have not been established.

CORTICOSTEROIDS — Use of corticosteroids in rheumatoid arthritis remains controversial. Prednisone 7.5 mg daily has been reported to reduce radiographic progression of disease in early rheumatoid arthritis, but rebound deterioration can occur when the dose is lowered or the drug is stopped. Many patients who have an inadequate response or are intolerant to other DMARDs benefit from 5 to 10 mg of prednisone per day or less. Low-dose prednisone may be especially useful in pregnant and elderly patients as an alternative to other DMARDs and in younger patients to control active disease temporarily until drugs with a slower onset of action can provide sufficient control. Use of corticosteroids in higher doses may be required to control severe systemic manifestations of rheumatoid arthritis, such as pericarditis or vasculitis. Intra-articular injection of a corticosteroid such as triamcinolone hexacetonide *(Aristospan)* often can relieve an acutely inflamed rheumatoid joint without systemic consequences (JA Hunter and TH Blyth, Drug Saf 1999; 21:353).

Adverse Effects — The adverse effects of systemic corticosteroids include osteoporosis, weight gain, fluid retention, cataracts, glaucoma, acceleration of atherosclerosis, avascular necrosis, poor wound healing, gastric ulcers and GI bleeding, hyperglycemia, hypertension, adrenal suppression and increased risk of infection. Even short-term corticosteroid use in low doses can cause bone loss; calcium and vitamin D supplements should be given concurrently (Medical Letter 2000; 42:29).

OTHER DRUGS — **Cyclosporine** (*Sandimmune, Neoral,* and others) alone or with methotrexate can be useful in some patients with refractory rheumatoid arthritis, but nephrotoxicity, drug interactions and cost have limited its use (JJ Cush et al, J Rheumatol 1999; 26:1176; *Medical Letter Handbook of Adverse Drug Interactions,* 2001, page 227). The antibiotic **minocycline** (*Minocin,* and others), reported to be modestly effective and well tolerated, may

be useful in early disease (JR O'Dell et al, Arthritis Rheum 1999; 42:1691). **Penicillamine** *(Depen, Cuprimine)* can be effective in patients with refractory rheumatoid arthritis and may delay progression of erosions, but its toxicity may be greater than that of methotrexate or sulfasalazine, and it is used uncommonly now. **Cyclophosphamide** (*Cytoxan*, and others) may be useful for treatment of severe rheumatoid vasculitis or refractory synovitis, but long-term use increases the risk of malignancy (CD Radis et al, Arthritis Rheum 1995; 38:1120).

COMBINATION THERAPY — Combination therapy may be more effective than individual drugs (JM Kremer et al, Ann Intern Med 2001; 134:695). In treatment of early rheumatoid arthritis, combination therapy with methotrexate, sulfasalazine and hydroxychloroquine, or methotrexate, sulfasalazine and prednisone (60 mg/day tapered in six weekly steps to 7.5 mg/day), was more effective than any of the individual drugs alone (T Möttönen et al, Lancet 1999; 353:1568; M Boers et al, Lancet 1997; 350:309). Clinical trials in patients with refractory rheumatoid arthritis have found that combinations of methotrexate with sulfasalazine and hydroxychloroquine, and methotrexate plus cyclosporine, were more effective than either methotrexate or the combination of sulfasalazine and hydroxychloroquine alone (JR O'Dell et al, N Engl J Med 1996; 334:1287; CM Stein et al, Arthritis Rheum 1997; 40:1843). In one small study in patients who had failed to respond to methotrexate alone, addition of leflunomide led to a response in about half (ME Weinblatt et al, Arthritis Rheum 1999; 42:1322). Addition of etanercept or infliximab has also been effective in patients with symptoms refractory to methotrexate alone.

PLASMAPHERESIS — Limited data suggest that plasmapheresis through a protein-A-containing column (*Prosorba* – Medical Letter 1999; 41:69) that adsorbs antibodies and circulating immune complexes may decrease symptoms in 30% to 40% of patients with severe refractory rheumatoid arthritis (RM Gendreau et al, Ther Apher 2001; 5:79). The optimal number of treatments, long-term effectiveness and safety of this approach are unknown.

CONCLUSION — Most Medical Letter consultants now begin treatment of rheumatoid arthritis with both an NSAID and a

disease-modifying anti-rheumatic drug (DMARD). COX-2 inhibitors have generally replaced older NSAIDs because they are less likely to cause gastrointestinal toxicity in patients not taking aspirin. Hydroxychloroquine is recommended for patients with mild arthritis and methotrexate is the DMARD of choice for moderate or severe disease. Sulfasalazine is an alternative to either drug. Combination regimens are useful in patients with symptoms refractory to initial therapy. The long-term safety and role of the new tumor-necrosis-factor inhibitors remains to be established.

COST OF SOME NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Drug	Usual dosage range for arthritis	Cost[1]
Salicylates, acetylated		
Aspirin, extended-release – average generic price	800 mg qid	$ 26.40
ZORprin (Knoll)		100.80
Aspirin, enteric-coated[2] – average generic price	975 mg qid	18.00
Ecotrin[2]		46.80
Salicylates, non-acetylated		
Choline magnesium trisalicylate – average generic price	3 grams/day in 1, 2 or 3 doses	52.80
Trilisate (Purdue Frederick)[3]		128.40
Sodium salicylate[2] – average generic price	3.6 to 5.4 grams/day in divided doses	6.06[4]
Salicylsalicylic acid (salsalate) – average generic price	3 to 4 grams/day in 2 or 3 doses	27.60
Disalcid (3M)		93.60
Mono-Gesic (Schwarz Pharma)		38.40
Celecoxib– *Celebrex* (Pharmacia)[3]	100 to 200 mg bid	87.60
Diclofenac – average generic price	150 to 200 mg/day in 2 or 3 doses	46.20
Voltaren (Novartis)		96.60
Arthrotec (Pharmacia)	50 mg diclofenac + 200 µg misoprostol tid-qid	134.10
extended-release – average generic price	100 mg once/day	77.10
Voltaren XR		94.50
Diflunisal – average generic price	500 to 1000 mg/day in 2 doses	38.40
Dolobid (Merck)		68.40
Etodolac – average generic price	300 mg bid-tid	48.00
Lodine (Wyeth-Ayerst)		94.20
Lodine XL	400 mg once/day	45.60
Fenoprofen – average generic price	300 to 600 mg tid-qid	27.00
Nalfon (Dista)		43.20