The Medical Letter®

On Drugs and Therapeutics

DRUGS OF CHOICE

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DRUGS OF CHOICE
from
THE MEDICAL LETTER

The Medical Letter, Inc.
New Rochelle, New York

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DRUGS FOR RHEUMATOID ARTHRITIS

Many different drugs are now used to treat rheumatoid arthritis. Aspirin and the other nonsteroidal anti-inflammatory drugs (NSAIDs) listed in the table on page 10 have immediate analgesic and anti-inflammatory effects, and they are relatively safe. Corticosteroids are anti-inflammatory and immunosuppressive; their place in the treatment of this disease is controversial. Slower-acting drugs currently used in the USA for treatment of rheumatoid arthritis include hydroxychloroquine, gold, penicillamine, methotrexate, and the cytotoxic drugs azathioprine and cyclophosphamide. These agents, which have no immediate analgesic effects, can control symptoms and may possibly delay progression of the disease, but they can cause severe adverse effects. NSAIDs are often used concurrently with the slower acting drugs, which may take months to produce a therapeutic response.

SALICYLATES — Aspirin in high doses is as effective as any other NSAID and much less expensive, but some patients cannot tolerate the gastrointestinal effects. Aspirin interferes with platelet function and can cause serious bleeding; this effect persists for four to seven days after the drug has been discontinued. Tinnitus and, rarely, hepatitis or renal damage can also occur with high-dosage aspirin therapy. Enteric-coated aspirin may be useful for patients who cannot tolerate the gastrointestinal effects of plain aspirin. Nonacetylated salicylates have less effect than aspirin on platelet function and may be safer for aspirin-sensitive patients, but may also have less anti-inflammatory effect.

OTHER NSAIDs — Many patients tolerate effective doses of other NSAIDs better than high-dose aspirin, but the newer drugs are much more expensive. There is no clinical evidence that any one of these agents is consistently more effective than any other, but some patients who do not respond to one NSAID may respond to another. Because of the risk of aplastic anemia, phenylbutazone (*Butazolidin*; and others) is no longer recommended for treatment of rheumatoid arthritis.

Adverse Effects – The nonsalicylate NSAIDs differ somewhat in their adverse effects, but there is no consensus among Medical Letter consultants on whether equally effective doses of any one are safer than any other. All NSAIDs can cause gastrointestinal toxicity, including peptic ulceration. Meclofenamate may cause a high incidence of diarrhea, which is sometimes severe. All NSAIDs can interfere with platelet function and prolong bleeding time; except with aspirin, this effect is quickly reversible when the drug is discontinued, but the combination of gastrointestinal irritation and prolonged bleeding time can cause serious gastrointestinal hemorrhage, especially in elderly patients (K Somerville et al, Lancet, 1:462, 1986).

NSAIDs decrease renal blood flow and can cause renal failure in some patients; diminished renal function and conditions associated with decreased intravascular volume, such as diuretic therapy, cirrhosis, or congestive heart failure, may increase the risk of renal damage. Sulindac may be less likely than other NSAIDs to cause adverse renal effects (MJ Dunn and C Patrono, eds, Am J Med, 81 Suppl 2B:1-132, 1986; DH Adams et al, Lancet, 1:57, 1986).

All NSAIDs can cause dizziness, anxiety, drowsiness, tinnitus, and confusion; these symptoms may occur initially and disappear with further use. Indomethacin may cause more severe CNS effects than other NSAIDs; depression, disorientation and, especially, severe headache occur frequently with higher doses. Aseptic meningitis has occurred in patients with lupus erythematosus or other connective tissue diseases who were taking ibuprofen, tolmetin, or sulindac, and has been reported with ibuprofen in patients without any connective tissue disease (JM Lawson and MJ Grady, West J Med, 143:386, 1985). Permanent hearing loss has been reported with piroxicam (DM Vernick and JH Kelly, Am J Otol, 7:97, 1986).

NSAIDs can cause mild hepatic dysfunction and, rarely, severe hepatitis. Pancreatitis has been reported (OL Haye et al, Ann Intern Med, 104:895, 1986). All NSAIDs can rarely cause blood dyscrasias; aplastic anemia has been reported with ibuprofen, fenoprofen, naproxen, indomethacin, tolmetin, and piroxicam. Asthmatic patients sensitive to aspirin could develop bronchospasm and respiratory failure with any NSAID, but not with nonacetylated salicylates. NSAIDs may interact with many other drugs (*Medical Letter Handbook of Adverse Drug Interactions*, 1987);

for example, they may decrease the effectiveness of diuretics, beta-blockers, and other antihypertensive drugs.

CORTICOSTEROIDS — Some patients with severe progressive rheumatoid arthritis may benefit from 5 to 10 mg/day of oral prednisone; those with vasculitis may require higher doses. Adverse effects of long-term systemic corticosteroids include osteoporosis, cataracts, poor wound healing, gastrointestinal bleeding, hyperglycemia, and hypertension (JP Seale and MR Compton, Med J Aust, 144:139, 1986). Intra-articular injection of corticosteroids may sometimes be helpful in treating a single acutely inflamed rheumatoid joint.

HYDROXYCHLOROQUINE ***(Plaquenil)*** — Many Medical Letter consultants have found the antimalarial hydroxychloroquine in doses of up to 6.5 mg/kg/day or 400 mg daily (whichever is less) effective for rheumatoid arthritis that has not responded adequately to nonsteroidal drugs. Antimalarials can cause severe and sometimes irreversible adverse effects on the eyes, skin, central nervous system, and bone marrow, but adverse effects are rare with recommended doses of hydroxychloroquine. Loss of visual acuity can generally be avoided if vision is monitored at six-month intervals by an ophthalmologist and the drug is discontinued promptly when signs of retinal toxicity first appear.

GOLD — Gold can be highly effective in mild to moderate rheumatoid arthritis and may delay or prevent progression of erosion in some patients. Gold sodium thiomalate *(Myochrysine)* and aurothioglucose *(Solganal)* are the two injectable preparations available in the USA. An oral preparation, auranofin *(Ridaura)*, appears to be less effective than injectable gold. In a 12-month controlled trial, auranofin was less effective, but also less toxic, than penicillamine (MC Hochberg, Ann Intern Med, 105:528, 1986).

Dosage – The usual dosage of injectable gold includes a test dose of 10 mg followed by 25 to 50 mg weekly for up to 20 weeks; some rheumatologists would continue until the total dose reaches 1500 mg. If a response occurs, treatment intervals are lengthened to every two weeks, then every three weeks, and then monthly. Patients should remain on monthly therapy for a prolonged period; discontinuing maintenance gold often results in a recurrence of arthritic symptoms, which may not remit when gold is reinstituted.

The adult dosage of auranofin is 3 mg twice a day or 6 mg once daily; treatment should be continued for at least six months and then, if the response is not satisfactory, dosage may be increased to 3 mg tid (if tolerated) for a further three months. If there is no favorable response, the drug should be discontinued.

Adverse Effects – Aurothioglucose, which is fat soluble, may be safer than gold thiomalate, which is water soluble and more likely to cause vasodilatation and "nitritoid" reactions; these reactions are uncommon and usually mild, but hypotension, syncope, and myocardial infarction have been reported. The most common adverse effects of gold salts are rash and proteinuria. Pruritus often precedes stomatitis and a diffuse rash, which can progress to generalized exfoliation; when pruritus occurs, the drug should be stopped, but it can often be restarted later at lower doses. Proteinuria, when it occurs, usually resolves when the drug is discontinued. Anaphylaxis, angioneurotic edema, glossitis, interstitial pneumonitis, leukopenia, thrombocytopenia, and aplastic anemia can also occur. Hepatitis and enterocolitis are rare, but severe ileitis has been reported (D Geltner et al, J Clin Gastroenterol, 8:184, 1986). Oral gold causes less mucocutaneous and renal toxicity than injectable gold, but more diarrhea and other gastrointestinal reactions.

PENICILLAMINE *(Depen, Cuprimine)* — Penicillamine in high doses can be effective in patients with refractory rheumatoid arthritis and may delay progression of erosions, but is also highly toxic. The manufacturer recommends beginning with a dose of 125 or 250 mg once a day and slowly (at one- to three-month intervals) increasing by 125- or 250-mg increments up to a total of 750 mg (rarely to 1000 or 1500 mg) per day. Penicillamine should be taken between meals because food decreases its absorption. The adverse effects of the drug, which are usually reversible, include fever, rash, hematuria, proteinuria, dysgeusia, aphthous ulcers, and thrombocytopenia. Pemphigus, myasthenia gravis, Goodpasture's syndrome, lupus-like illness, cholestatic jaundice, fatal bronchiolitis, and severe bone marrow depression can also occur. Penicillamine is teratogenic and should not be used during pregnancy.

METHOTREXATE (*Mexate*; and others) — Controlled trials have now established the effectiveness of methotrexate for rheumatoid arthritis. It can be given initially in a dosage of 2.5 mg every 12 hours for three doses

each week, increasing slowly at monthly intervals to 15 mg per week. The drug has also been given once weekly, beginning with a 5-mg dose and increasing gradually (HJ Williams et al, Arthritis Rheum, 28:721, 1985; PA Andersen et al, Ann Intern Med, 103:489, 1985; ME Weinblatt et al, N Engl J Med, 312:818, 1985). Methotrexate can cause hepatic toxicity, interstitial pneumonitis, bone marrow suppression, and gastrointestinal ulceration and bleeding (RF Willkens, Ann Intern Med, 103:612, 1985; JH Klippel and JL Decker, N Engl J Med, 312:853, 1985). It should not be given to patients with renal insufficiency. Aspirin and possibly other NSAIDs may increase the toxicity of methotrexate by slowing its rate of excretion.

AZATHIOPRINE ***(Imuran)*** — Azathioprine, a cytotoxic drug, is effective in some patients with refractory rheumatoid arthritis, but nausea, vomiting, abdominal pain, hepatitis, and reversible bone marrow depression can occur. One 24-week study including 70 patients treated with 1.25 to 1.5 mg/kg/day of azathioprine and 64 patients taking 10 to 12 mg/kg/day of penicillamine found the two drugs equally effective (HE Paulus et al, Arthritis Rheum, 27:721, 1984).

CYCLOPHOSPHAMIDE ***(Cytoxan; Neosar)*** — Cyclophosphamide, another cytotoxic drug, has been used to treat patients with refractory rheumatoid arthritis, such as those with severe vasculitis. It can cause serious toxic effects, including alopecia, hemorrhagic cystitis, bone marrow depression, sterility, bladder cancer, and other malignant diseases.

COST OF SOME NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Drug	Usual Dosage Range for Arthritis	Cost of 30 Days Treatment*
Aspirin – average generic price (range: $1.69 to $7.74)	3.6 to 5.4 grams/day	$ 3.17
Aspirin, enteric-coated average generic price (range: $2.38 to $8.82)	3.6 to 7.2 grams/day	4.61
Aspirin, buffered		
Arthritis Pain Formula (Whitehall)	2 tablets tid-qid	9.38
Arthritis Strength Bufferin (Bristol-Myers)	2 tablets q4h	18.61
Aspirin, controlled release		
8 Hour Bayer (Glenbrook)	2 tablets q8h	8.46
Zorprin (Boots)	1600 mg bid	16.56
Non-acetylated salicylates		
Magnesium salicylate – *Magan* (Adria)	2 tablets tid-qid	33.01
Choline salicylate – *Arthropan* (Purdue Frederick)	4.8 to 7.2 grams/day	22.20
Choline magnesium salicylate *Trilisate* (Purdue Frederick)	3 grams/day	35.52
Sodium salicylate – average generic price (range: $1.98 to $8.78)	3.6 to 5.4 grams/day	3.67
Salicylsalicylic acid (salsalate)	3 to 4 grams/day	
Disalcid (Riker)		35.16
Mono-Gesic (Central)		20.40
Fenoprofen – *Nalfon* (Dista)	300 to 600 mg tid-qid	28.69
Ibuprofen	600 to 800 mg tid-qid	
Motrin (Upjohn)		15.58
Rufen (Boots)		10.48
Advil (Whitehall)†		12.00
Nuprin (Bristol-Myers)†		12.00
Indomethacin-average generic price (range: $8.33 to $26.42)	25 to 50 mg tid	15.88
Indocin (Merck)		33.39
Indocin SR (Merck)	75 mg once/day or bid	26.85
Ketoprofen – *Orudis* (Wyeth)	50 to 75 mg tid-qid	30.86
Meclofenamate sodium – *Meclomen* (Parke-Davis)	200 to 400 mg/day in 3 or 4 doses	43.34
Naproxen – *Naprosyn* (Syntex)	250 to 500 mg bid	29.89
Naproxen sodium – *Anaprox* (Syntex)	275 mg bid or tid	28.95
Piroxicam – *Feldene* (Pfizer)	20 mg daily	38.54
Sulindac – *Clinoril* (Merck)	150 to 200 mg bid	37.86
Tolmetin – *Tolectin* (McNeil)	200 to 400 mg tid	26.64

* Cost is to the pharmacist for 30 days' treatment with the lowest usual dosage, based on listings in *Drug Topics Red Book* and March 1987 *Update*; Average Wholesale Price used when available. The cost to the patient will be higher.

† Available without prescription in 200-mg tablets for limited use

DRUGS FOR ASTHMA

Patients with intermittent asthma are often free of the disease for periods of weeks or months; such patients need drugs only to relieve symptoms when they develop. Patients with chronic asthma have recurrent or persistent symptoms that interfere with sleep and other activities; they need a continuous regimen. The treatment of asthma in the hospital is not discussed here.

ADRENERGIC DRUGS — The effects of adrenergic (sympathomimetic) drugs can be broadly divided into vasoconstriction (alpha receptors), cardiac stimulation ($beta_1$ receptors), bronchodilatation ($beta_2$ receptors), skeletal muscle tremors ($beta_2$ receptors), hyperglycemia ($beta_2$ receptors), and hypokalemia. The newer beta-adrenergic stimulants, such as albuterol *(Proventil; Ventolin)* or terbutaline (*Brethine*; and others), are $beta_2$-selective; they produce bronchodilatation with less cardiac stimulation than older sympathomimetics such as isoproterenol (*Isuprel*; and others), and they have a longer duration of action.

Both the effectiveness and adverse effects of adrenergic drugs vary with the route of administration; inhalation provides the most rapid relief of acute asthmatic symptoms with the fewest adverse effects. A metered-dose inhaler is the usual method of delivery, but patients with severe airway obstruction and children too young to use an inhaler may benefit from nebulized solutions driven by oxygen or an air compressor. Spacer devices (aerosol-holding chambers) can be attached to a metered-dose inhaler to improve delivery in patients with chronic obstructive pulmonary disease who cannot inhale all of the medication in one breath, and for children and others who have difficulty coordinating discharge of the inhaler with inhalation.

Except when severe dyspnea prevents effective delivery, subcutaneous injection is generally no more effective than inhalation and causes more frequent adverse effects, including tremor, tachycardia, nausea, vomiting, and headache. Oral $beta_2$-selective agonists are less effective and slower acting than the same drugs given by inhalation and frequently

cause tremor, while inhaled drugs generally do not, but oral drugs may be useful for young children who cannot use an inhaler. Any beta-adrenergic agonist may become less effective with continued use (HS Nelson, J Allergy Clin Immunol, 77:771, 1986).

Ephedrine has been used for treatment of asthma for many years, particularly with theophylline and other drugs in oral fixed-dose combinations such as *Tedral* and *Marax*. Since the newer adrenergics have fewer central-nervous-system-stimulating effects, there is no longer any good reason to prescribe ephedrine.

Epinephrine (*Adrenalin*; and others) is available for inhalation or injection. Inhaled epinephrine, which is available without a prescription, is much shorter-acting than inhaled albuterol or other prescription beta-agonists. Subcutaneous injection of epinephrine is more toxic and generally no more effective than inhalation of a $beta_2$-selective drug.

Isoproterenol (*Isuprel*; and others) and **isoetharine** *(Bronkometer; Bronkosol)* are available for inhalation. Both drugs have a short duration of action and cause cardiac stimulation.

Metaproterenol *(Alupent; Metaprel)* is less $beta_2$-selective than albuterol or terbutaline and causes more cardiac stimulation, especially in patients with hypoxia. It is available for inhalation and oral use.

Albuterol *(Proventil; Ventolin)* is a $beta_2$-selective agonist available for inhalation and oral use.

Terbutaline *(Brethine; Brethaire; Bricanyl)* is the only $beta_2$-selective agonist available in the USA for subcutaneous injection as well as inhalation and oral use. Terbutaline is similar to albuterol, but terbutaline tablets have been reported to cause more intense muscle tremors early in therapy (JW Jenne et al, Am Rev Respir Dis, 134:708, 1986).

Bitolterol mesylate *(Tornalate)* is the newest $beta_2$-selective agonist available in a metered dose inhaler (Medical Letter, 27:46, 1985). A prodrug that is hydrolyzed by lung esterases to colterol, the active moiety, it may have a slightly longer duration of action than albuterol.

Fenoterol *(Berotec)*, which is similar to albuterol, is available in Canada and Europe, but not in the USA (N Svedmyr, Pharmacotherapy, 5:109, 1985).

THEOPHYLLINE — Oral theophylline has limited usefulness for treatment of acute symptoms in patients with intermittent asthma. It is a less potent bronchodilator than subcutaneous or inhaled adrenergic drugs and, in patients who have not been taking the drug continuously, causes transient adverse effects even at low serum concentrations. One study in 40 patients with acute asthma receiving a nebulized beta-agonist hourly for three hours found that therapeutic serum concentrations of theophylline did not add any benefit and increased the frequency of adverse effects (D Siegel et al, Am Rev Respir Dis, 132:283, 1985). In patients with chronic asthma, however, theophylline effectively decreases the frequency and severity of asthmatic symptoms and can decrease steroid requirements in corticosteroid-dependent asthma.

Toxicity – Patients with mild symptoms may benefit from theophylline serum concentrations of less than 10 mcg/ml. At concentrations of 10 to 20 mcg/ml, jitteriness is common, and poor school performance and behavioral abnormalities can occur in children (GS Rachelefsky et al, Pediatrics, 78:1133, 1986). At serum concentrations higher than 20 mcg/ml, the frequency and severity of adverse effects increase progressively; these include nausea, vomiting, diarrhea, headache, nervousness, tachycardia, insomnia, cardiac arrhythmias, and death. The number of reports of severe theophylline toxicity has increased markedly in recent years, particularly in infants and in older patients with sustained fever, who metabolize theophylline at a slower rate.

Rates of metabolism – Theophylline is metabolized at varying rates by the liver; the half-life averages 8 hours (range 3 to 15) for non-smoking adults and 3.7 hours (range 2 to 9) for children more than one year old. The half-life is very long in the newborn and decreases progressively during the first year of life. Because the rate at which patients metabolize theophylline varies, an "average dose" will produce a wide range of steady-state serum concentrations; dosage therefore must be individualized on the basis of serum measurements to achieve maximum benefit and safety. Heart failure, liver dysfunction, chronic obstructive pulmonary disease, or sustained fever can slow theophylline metabolism and