DRUGS OF CHOICE

from

The Medical Letter®

for

Arthritis, Asthma, Cancer, Cardiac Arrhythmias, Epilepsy, Hypertension, Migraine, and Psychiatric Disorders

Revised Edition 1985

DRUGS OF CHOICE

from

THE MEDICAL LETTER

The Medical Letter, Inc.
New Rochelle, New York

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New Rochelle, New York 10801

THE MEDICAL LETTER® on Drugs and Therapeutics is an independent nonprofit publication providing unbiased critical evaluations of drugs in terms of their effectiveness, adverse effects and possible alternative medications. It carries no advertising and is supported entirely by subscription fees.

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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 9 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, injectable gold, penicillamine, and the cytotoxic drugs methotrexate, 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. An NSAID is often used concurrently with the slower acting drugs, which sometimes take weeks or months to produce a therapeutic response.

ASPIRIN ***(Acetylsalicylic Acid)*** – Aspirin is as effective as any other NSAID and much less expensive, but some patients cannot tolerate the gastrointestinal effects of high doses. Tinnitus, serious bleeding and, rarely, hepatitis or renal damage can also occur with high-dosage aspirin therapy. In older patients and others with decreased renal function, aspirin can cause hearing loss.

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 are less likely to cause bleeding.

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; some patients who do not respond to one NSAID may respond to another. Phenylbutazone *(Butazolidin)* and

oxyphenbutazone *(Tandearil)* are no longer recommended for initial treatment of rheumatoid arthritis and are not included in this discussion.

Adverse Effects — The non-salicylate 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; the combination of gastrointestinal irritation and prolonged bleeding time can cause serious gastrointestinal hemorrhage.

NSAIDs, because they inhibit prostaglandin synthesis, decrease renal blood flow and can cause renal failure in patients with compromised renal function. Renal papillary necrosis, interstitial nephritis, acute renal shutdown, and potentially fatal hyperkalemia can also occur (WB Reeves et al, Arch Intern Med, 144:1943, Oct 1984; KP Miller et al, Arch Intern Med, 144:2414, Dec 1984). All NSAIDs can cause central-nervous-system (CNS) toxicity, such as 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 (DR Perera et al, Ann Intern Med, 100:619, 1984; JP Quinn et al, Neurology, 34:108, 1984).

NSAIDs can cause mild hepatic dysfunction and, rarely, severe hepatitis. All NSAIDs can cause blood dyscrasias; aplastic anemia has been reported with ibuprofen, fenoprofen, naproxen, indomethacin, tolmetin, and piroxicam. Allergic and other skin reactions may be especially frequent with piroxicam and meclofenamate (RS Stern and M Bigby, JAMA, 252:1433, Sept 21, 1984). Asthmatic patients sensitive to aspirin could develop bronchospasm and respiratory failure with any NSAID.

CORTICOSTEROIDS — Some patients with severe progressive rheumatoid arthritis, especially those with vasculitis, may benefit from 5

to 10 mg/day of oral prednisone. In one study, patients taking up to 20 mg daily of prednisolone had good preservation of function and few adverse effects over a ten-year period (R Million et al, Lancet, 1:812, 1984), but lower dosage is preferable. Adverse effects of systemic corticosteroids include osteoporosis, cataracts, poor wound healing, and gastrointestinal bleeding.

HYDROXYCHLOROQUINE *(Plaquenil)* — Many Medical Letter consultants have found the antimalarial hydroxychloroquine in dosage of up to 400 mg daily effective in rheumatoid arthritis unresponsive to nonsteroidal drugs. Some antimalarials can cause severe and sometimes irreversible adverse effects on the eye, skin, central nervous system, and bone marrow, but adverse effects are rare with recommended doses of hydroxychloroquine. Loss of visual acuity can be avoided if vision is monitored at six-month intervals and the drug is discontinued promptly when signs of retinal toxicity first appear (DR Tobin et al, Arch Ophthalmol, 100:81, 1982; RI Rynes, Am J Med, Suppl:35, July 18, 1983).

GOLD — Injectable 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, is an investigational drug in this country (JD O'Duffy and HS Luthra, Drugs, 27:373, 1984; V Wright, Br Med J, 289:858, Oct 6, 1984).

Dosage – The usual dosage of injectable gold starts with a test dose of 10 mg followed by 25 to 50 mg weekly for a period of up to twenty weeks. 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.

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 a diffuse rash, sometimes accompanied by stomatitis, which can progress to generalized exfoliation; when pruritus occurs, the drug should be stopped, but it often can be restarted later at lower doses. Proteinuria, when it occurs, is usually due to glomerulonephritis; it usually resolves when the drug is discontinued. Anaphylaxis, angioneurotic edema, glossitis, interstitial pneumonitis, leukopenia, thrombocytopenia, and aplastic anemia can also occur. Enterocolitis and hepatitis are rare.

PENICILLAMINE *(Depen, Cuprimine)* — Penicillamine in high doses can be highly effective in patients with refractory rheumatoid arthritis and may delay progression of erosions, but is also highly toxic (Medical Letter, 20:73, 1978). The manufacturer recommends beginning with a dose of 125 or 250 mg once a day and slowly (over one to three-month intervals) increasing by 125- or 250-mg increments, working up to 750 mg (rarely to 1000 or 1500 mg) per day. Food decreases absorption of penicillamine. The adverse effects of penicillamine, which are usually reversible, include fever, rash, hematuria, proteinuria, dysgeusia and aphthous ulcers. Pemphigus, myasthenia gravis, Goodpasture's syndrome, lupus-like illness, fatal bronchiolitis, and severe bone marrow depression can also occur. Cholestatic jaundice has been reported. Penicillamine is teratogenic and should not be used during pregnancy.

METHOTREXATE (*Mexate*; and others)— Medical Letter consultants report that soon-to-be published studies with the folic acid antagonist methotrexate have shown favorable results in some patients with rheumatoid arthritis. One published six-week trial in 48 patients found weekly doses of 10 to 25 mg more effective than placebo for refractory disease (RN Thompson et al, J Rheumatol, 11:760, 1984). Methotrexate is teratogenic and can cause severe hepatic toxicity, interstitial pneumonitis, bone marrow suppression, and severe gastrointestinal ulceration and bleeding. It has not been approved for treatment of rheumatoid arthritis by the US Food and Drug Administration (FDA).

AZATHIOPRINE *(Imuran)* — Azathioprine, a cytotoxic drug, is effective in some patients with refractory rheumatoid arthritis, but it can cause severe adverse effects. In 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, the two drugs were equally effective. Eighteen

of 102 patients taking azathioprine withdrew from the study because of nausea, vomiting, abdominal pain, hepatitis, or leukopenia (HE Paulus et al, Arthritis Rheum, 27:721, 1984). Azathioprine can cause severe bone marrow depression and is probably carcinogenic.

CYCLOPHOSPHAMIDE ***(Cytoxan; Neosar)*** — Cyclophosphamide, another cytotoxic drug, has been used to treat refractory rheumatoid arthritis, but it can also cause severe toxic effects, including alopecia, hemorrhagic cystitis, severe bone marrow depression, sterility, bladder cancer, and other malignant diseases. Cyclophosphamide has not been approved for treatment of rheumatoid arthritis by the US FDA.

DRUG INTERACTIONS — Most of the drugs used to treat rheumatoid arthritis can interact adversely with other drugs taken at the same time (see *The Medical Letter Handbook of Adverse Drug Interactions*, 1985).

SOME NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Drug	Usual Dosage Range for Arthritis	Cost of 30 Days' Treatment*
Aspirin — average generic price	3.6-5.4 grams/day	$ 2.09
Bayer		5.40
A.S.A. (Lilly)		3.20
A.S.A. Pulvules (Lilly)		9.03
Empirin (Burroughs Wellcome)		5.99
Measurin (Breon)		22.20
St Joseph Adult Aspirin (Plough)		3.57
Aspirin, enteric-coated		
average generic price	3.6-5.4 grams/day	3.24
A.S.A. Enseals (Lilly)		8.92
Cosprin (Glenbrook)	650 mg q4h	11.05
Easprin (Parke, Davis)	1 gram tid-qid	10.77
Ecotrin Maximum Strength (SKF)	1 gram q6h	16.46
Aspirin, buffered		
Arthritis Strength Bufferin (Bristol-Myers)	2 tablets q4h	15.59
Arthritis Pain Formula (Whitehall)	2 tablets tid-qid	6.64
Aspirin, controlled release		
Zorprin (Boots)	1600 mg bid	12.24

(continued)

Drug	Usual Dosage Range for Arthritis	Cost of 30 Days' Treatment*
Non-acetylated salicylates		
Magnesium salicylate		
Magan (Adria)	2 tablets tid-qid	25.85
Choline salicylate		
Arthropan (Purdue Frederick)	4.8-7.2 grams/day	19.11
Choline magnesium salicylate		
Trilisate (Purdue Frederick)	3 grams/day	24.97
Sodium salicylate — average generic price	3.6-5.4 grams/day	2.71
Diflunisal		
Dolobid (Merck)	250-500 mg bid	29.40
Salicylsalicylic acid (salsalate)	3-4 grams/day	
Disalcid (Riker)		25.63
Mono-Gesic (Central)		18.00
Fenoprofen	300-600 mg tid-qid	
Nalfon (Dista)		22.36
Ibuprofen	400-600 mg tid-qid	
Motrin (Upjohn)		15.58
Rufen (Boots)		9.72
Advil (Whitehall)†		12.01
Nuprin (Bristol-Myers)†		13.21
Indomethacin-average generic price	25 mg tid-50 mg qid	18.18
Indocin (Merck)		26.62
Indocin SR (Merck)	75 mg once/day	22.61
Meclofenamate sodium	200-400 mg/day in 3-4 doses	
Meclomen (Parke, Davis)		33.05
Naproxen – *Naprosyn* (Syntex)	250-500 mg bid	26.86
Naproxen sodium – *Anaprox* (Syntex)	275 mg bid-tid	26.00
Piroxicam	20 mg daily	
Feldene (Pfizer)		34.41
Sulindac	150-200 mg bid	
Clinoril (Merck)		30.05
Tolmetin	200-600 mg tid	
Tolectin (McNeil)		23.28

* Cost is to the pharmacist for 30 days' treatment with the lowest usual dosage, based on listings in *Drug Topics Red Book* and February 1985 *Update*; Average Wholesale Price used when available. The cost to the patient will be higher.

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

DRUGS FOR ASTHMA

Several advances have been made in recent years in the prevention and treatment of asthma. Isoetharine, metaproterenol, terbutaline and albuterol are adrenergic drugs that offer some advantages over the previously available epinephrine, isoproterenol and ephedrine. Use of spacers or extension tubes that can be attached to the mouthpieces of pressurized aerosol devices has made administration of adrenergic drug aerosols more efficient for some patients. New, slow-release formulations of theophylline may be particularly convenient for oral administration (Medical Letter, 26:1, 1984), and studies of theophylline plasma concentrations have led to more effective and safer use of aminophylline and other theophylline salts. Another important development has been the increased use of topical glucocorticoids that can be inhaled and often substituted for systemic glucocorticoids (Medical Letter, 27:5, 1985).

ADRENERGIC DRUGS — Adrenergic drugs can cause vasoconstriction (alpha receptors), cardiac stimulation ($beta_1$ receptors), and bronchodilatation ($beta_2$ receptors).

Epinephrine (*Adrenalin*; and others) **and Isoproterenol** (*Isuprel*; and others) — Both epinephrine and isoproterenol are catecholamines that have been used to relieve the symptoms of acute asthma. Their duration of action is short, and they are inactive when taken orally. Epinephrine has vasoconstrictive, cardiac, and bronchial activity, while isoproterenol acts on the heart and bronchi. Epinephrine is available for injection or inhalation; isoproterenol is usually given by inhalation. Both produce bronchodilatation by causing relaxation of smooth muscle, and epinephrine may possibly also reduce airway obstruction by constricting blood vessels in the bronchial mucosa and thereby decreasing congestion and edema. Epinephrine raises blood pressure, and high doses of either epinephrine or isoproterenol can precipitate attacks of angina pectoris and cause cardiac arrhythmias.

Ephedrine — Ephedrine, which is not a catecholamine, has long been given orally for asthma, particularly with theophylline and other drugs in fixed-dose combinations, such as *Tedral* and *Marax*. Since the newer adrenergics have fewer central-nervous-system (CNS)-stimulating effects, there is no longer any good reason to prescribe ephedrine.

Isoetharine *(Bronkometer; Bronkosol)* — Isoetharine is a relatively bronchoselective catecholamine. Like others in this group, it may have cardiac and CNS-stimulating effects when given as an aerosol.

Metaproterenol *(Alupent; Metaprel)* — Metaproterenol (orciprenolol in Canada) is not a catecholamine; consequently, it is degraded more slowly than isoproterenol or isoetharine and has a longer duration of action. It causes less cardiac stimulation than isoproterenol. Tremor is a common adverse effect of the drug, particularly after oral administration.

Terbutaline *(Brethine; Bricanyl; Brethaire)* — Terbutaline, a noncatecholamine bronchoselective drug that is longer acting than metaproterenol, causes relatively little cardiac stimulation when taken orally. Subcutaneous injection may, however, cause considerable cardiac stimulation. Tremor, which tends to diminish after a week or two, is the most frequent adverse effect after oral administration.

Albuterol (salbutamol; *Proventil; Ventolin*) — Albuterol is the newest bronchoselective agent to be introduced in the USA. It is also a noncatecholamine that is orally effective, long-acting, and causes little direct cardiac stimulation. As with metaproterenol and terbutaline, tremor is the most common adverse effect of oral use.

Fenoterol *(Berotec)* — Fenoterol, which is similar to albuterol, is available in Canada and Europe, but not in the USA (P König and DJ Hurst, Arch Intern Med, 143:1361, 1983).

THEOPHYLLINE AND ITS SALTS — The effectiveness of theophylline salts for bronchodilatation depends entirely on their content of anhydrous theophylline. Since the difference between therapeutic and toxic doses of theophylline may be small, it is best to begin with a low dose and increase as needed. Plasma concentrations should generally be monitored; the

optimal range is between 10 and 20 μg per ml, although some patients achieve good control of asthma symptoms at lower concentrations.

The development of slow-release preparations has made possible maintenance of therapeutic plasma concentrations by giving the drug every 12 or, at most, every eight hours. The safety and reliability of once-a-day formulations has not been established (WH Barr, Pharmacotherapy, 4:167, 1984). Many factors, including treatment with cimetidine *(Tagamet)*, erythromycin, and other drugs, congestive heart failure, liver disease, acute viral infections, and possibly even influenza vaccine can retard theophylline metabolism and thereby increase the risk of toxicity. Metabolic degradation is also slow in young infants; it is relatively fast in young children, but gradually slows toward the adult rate after the age of ten. Theophylline-containing suppositories may be erratically absorbed and should not be used; theophylline in rectal solutions is more reliably absorbed. Smokers may require higher dosage, since they metabolize the drug faster.

Adverse effects of theophylline include headache, insomnia, nervousness, abdominal discomfort, nausea, and vomiting. More severe adverse effects include seizures and cardiac arrhythmias. For IV administration aminophylline should be diluted and given over 30 minutes. Convulsions can occur with oral or IV use without premonitory symptoms.

CROMOLYN SODIUM *(Intal)* — Cromolyn can prevent the symptoms of asthma. The drug has little bronchodilator effect and no anti-inflammatory effects, and is not effective for treatment of acute asthmatic attacks or status asthmaticus. In patients with attacks precipitated by exercise, the drug may be effective when given shortly before exercising. Adverse effects of cromolyn are uncommon, but may include severe bronchospasm, cough, and irritation of the throat and trachea.

GLUCOCORTICOIDS — Oral glucocorticoids (steroids) are highly effective for treatment of asthma, but because of their potential adverse effects, they should not be used for asthma that can be controlled by other means. Adverse effects of systemic steroids include suppression of growth, osteoporosis, aggravation of diabetes, aseptic bone necrosis, and adrenocortical suppression.