Drugs Used to Treat Inflammation and Associated Pain

Pharmacology 659
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Nonsteroidal Anti-inflammatory Drugs

Disease Modulating Anti-rheumatic Drugs

Nonopioid Analgesics

Drugs Used to Treat Gout
**Acute inflammation** is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue.

**Chronic inflammation**, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.
## Comparison of Acute and Chronic Inflammation

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causative agent</strong></td>
<td>Pathogens, injured tissues</td>
<td>Persistent acute inflammation due to non-degradable pathogens, persistent foreign bodies, or autoimmune reactions</td>
</tr>
<tr>
<td><strong>Major cells involved</strong></td>
<td>Neutrophils, mononuclear cells (monocytes, macrophages)</td>
<td>Mononuclear cells (monocytes, macrophages, lymphocytes, plasma cells), fibroblasts</td>
</tr>
<tr>
<td><strong>Primary mediators</strong></td>
<td>Vasoactive amines, eicosanoids</td>
<td>IFN-γ and other cytokines, growth factors, reactive oxygen species, hydrolytic enzymes</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Few days</td>
<td>Up to many months, or years</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Resolution, abscess formation, chronic inflammation</td>
<td>Tissue destruction, fibrosis</td>
</tr>
</tbody>
</table>
Diseases Associated with Chronic Inflammation and Pain

Osteoarthritis
Rheumatoid arthritis
Bursitis
Gout
Systemic lupus erythematosis
Fibromyalgia
Osteoporosis
Inflammation of Joints

Inflammation is characterized by

- Redness
- Swollen joints that are warm to touch
- Joint pain
- Joint stiffness
- Loss of joint function
Inflammation

Inflammation might also be associated with general “flu-like” symptoms including:

- Fever
- Chills
- Fatigue/loss of energy
- Headaches
- Loss of appetite
- Muscle stiffness
Treatment of Pain

• Opioids
• Antidepressants and antiepileptic drugs
  • Amitriptyline (tricyclic)
  • Gabapentin (antiepileptic)
• Other Adjuvant & Atypical Analgesic Agents
  • Orphenadrine (antihistamine)
  • Scopolamine, atropine (anticholinergic)
• Non-steroidal anti-inflammatory drugs
Synthesis of Arachidonic Acid

Stimulus → Disturbance of cell membranes → Phospholipids

- Phospholipase inhibitors
- Corticosteroids

Arachidonic acid → Fatty acid substitution (diet)

Phospholipase
Alteration of vascular permeability, bronchial constriction, increased secretions

Phagocyte attraction, activation

Colchicine

Inflammation, pain, swelling

Arachidonic acid

Lipoxygenase inhibitors

Lipoxygenase

Lipoxygenase inhibitors

LTC₄/D₄/E₄

Leukotrienes

Receptor antagonists

LTC₄/D₄/E₄

Prostaglandins

Cyclooxygenase

Phagocyte attraction, activation

Inflammation, pain, swelling

Alteration of vascular permeability, bronchial constriction, increased secretions

LTB₄

Arachidonic acid

Cyclooxygenase

Prostaglandins

Colchicine

Lipoxygenase inhibitors

Lipoxygenase
Arachidonic acid

Thromboxane

Prostacyclin

Prostaglandins

Leucocyte modulation

Alteration of vascular permeability, bronchial constriction, increased secretions

Inflammation, pain, swelling

Cyclooxygenase

NSAID, ASA
Arachidonic acid

- COX-1: Constitutive
  - Homeostatic functions
    - GI track, Renal function
    - Platelet function
    - Macrophage differentiation

- COX-2: Induced
  - Inflammation
  - Cytokines, IL-1, TNF, growth factors
  - Glucocorticoids, Cytokines, IL-1
<table>
<thead>
<tr>
<th>Site</th>
<th>COX Form</th>
<th>Product</th>
<th>Effect</th>
<th>Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric Mucosa</td>
<td>COX-1</td>
<td>PGE₂, PGI₂</td>
<td>Mucous production, HCO₃⁻ secretion, mucosal blood flow, ↓ H⁺ secretion</td>
<td>Gastric ulcer</td>
</tr>
<tr>
<td>Platelets</td>
<td>COX-1</td>
<td>TAX₂</td>
<td>↑ Platelet aggregation</td>
<td>↓ Risk of MI ↑ Bleeding tendencies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PGI₂</td>
<td>↓ Platelet aggregation, ↓ Adhesion to endothelium</td>
<td>↑ Platelet aggregation ↑ Adhesion to endothelium</td>
</tr>
<tr>
<td>Lungs</td>
<td>COX-1</td>
<td>PGE₂</td>
<td>Bronchodilation</td>
<td>Bronchoconstriction</td>
</tr>
<tr>
<td>Kidney</td>
<td>COX-1, COX-2</td>
<td>PGE₂, PGI₂</td>
<td>Renal vasodilation, Maintenance of function</td>
<td>Renal dysfunction Na⁺ and H₂O retention</td>
</tr>
<tr>
<td>Damaged Tissues</td>
<td>COX-2</td>
<td>PGE₂</td>
<td>Inflammation, pain</td>
<td>↓ Inflammation Analgesia (peripheral)</td>
</tr>
<tr>
<td>Brain</td>
<td>COX-2</td>
<td>PGE₂</td>
<td>Fever</td>
<td>Antipyretic effect</td>
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</tbody>
</table>
Other Mechanisms of Action

• Inhibition of chemotaxis
• Down-regulation of interleukin-1 synthesis
• Decreased production of free radicals and superoxide
• Interference with calcium-mediated intracellular events
Other Actions

- Decrease sensitivity of blood vessels to histamine and bradykinin
- Affect lymphokine production from T lymphocytes
- Reverse the vasodilation of inflammation
- Inhibit platelet aggregation (except COX-2 selective agents)
- Are all gastric irritants producing ulcers and bleeding
- All produce nephrotoxicity
- All can produce hepatotoxicity
- Do not alter the course of any rheumatic disorder
- Reduce incidence of colon cancer (by almost 50%)
Non-steroidal Anti-Inflammatory Drugs (NSAIDS)

- Weak organic acids
- Well absorbed, can be taken with food
- Highly metabolized by phase I and phase II mechanisms
- Metabolism proceeds largely by hepatic CYP3A and CYP2C enzymes
- Excretion is mainly by the kidneys
- Biliary excretion and reabsorption related to GI irritation
- Most are highly protein bound, usually to albumin
- All can be found in synovial fluid
Adverse Effects of NSAIDS

Cardiovascular

- Fluid retention
- Hypertension
- Edema
- Congestive heart failure (rare)
Adverse Effects of NSAIDS

Gastrointestinal

• Abdominal pain
• Dysplasia
• Nausea
• Vomiting
• Ulcers (rare)
• Bleeding (rare)
Adverse Effects of NSAIDS

Hematologic (rare)

- Thrombocytopenia
- Neutropenia
- Aplastic anemia
Adverse Effects of NSAIDS

Renal

- Renal insufficiency
- Renal Failure
- Hyperkalemia
- Proteinuria
Adverse Effects of NSAIDS

Central Nervous System

- Headaches
- Tinnitus
- Dizziness
Adverse Effects of NSAIDS

Other

- Hepatic: Abnormal liver function tests and rare liver failure
- Pulmonary: Asthma
- Rashes: All types, pruritus
Therapeutic Uses

• Rheumatoid arthritis
• Seronegative spondyloarthropathies
• Osteoarthritis
• Localized musculoskeletal syndromes (sprains, strains, low back pain)
• Gout (except tolmetin)
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
Acetylsalicylic acid (Aspirin, ASA)

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<table>
<thead>
<tr>
<th>t \frac{1}{2} (hours)</th>
<th>Elimination by kidney</th>
<th>Antiinflammatory Dose</th>
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</thead>
<tbody>
<tr>
<td>0.25</td>
<td>&gt;2%</td>
<td>1200 -1500 mg tid</td>
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</table>
Therapeutic Uses

- Headache
- Pain
- Fever
- Prevention of heart attacks and strokes
- Coronary and carotid arteries, bypasses and stents
- Other uses
Metabolism of Salicylates

Aspirin

Acetic acid

Conjugation with glucuronic acid

Salicylate

Conjugation with glycine

Ester and ether glucuronides

Salicyluric acid

Oxidation

Free Salicylate

Gentisic acid 1%
Aspirin overdose

mild intoxication

- Nausea and vomiting
- Abdominal pain
- Lethargy
- Tinnitus
- Dizziness
Aspirin overdose
Severe Intoxication

- Hyperthermia
- Tachypnea
- Respiratory alkalosis
- Metabolic acidosis
- Hypokalemia
- Hypoglycemia
- Hallucinations
- Confusion
- Seizures
- Cerebral edema
- Coma
- Cardiopulmonary arrest
  usually due to pulmonary edema
Aspirin overdose

- Acute overdose has a mortality rate of 2%
- Chronic overdose has a mortality rate of 25%
- Chronic overdose might be especially severe in children

**Toxicity is managed with:**

- activated charcoal
- intravenous dextrose and normal saline
- sodium bicarbonate
- dialysis
Symptoms of Aspirin overdose

- Restlessness
- Irritability
- Excessive and unorganized talking
- Fear or nervousness
- Dizziness
- Confusion
- Abnormally excited mood
- Hallucinations
- Drowsiness
- Loss of consciousness

Systemic:
- Fever

- Double vision
- Uncontrollable shaking
- Seizures
- Burning throat pain
- Vomiting
- Pain
- Decreased urination
Reye’s Syndrome

Stage I

Persistent, heavy vomiting that is not relieved by eating
Generalized lethargy
General mental symptoms, e.g. confusion
Nightmares
High Fever

Stage II

Stupor caused by minor brain inflammation
Hyperventilation
Fatty liver (found by biopsy)
Hyperactive reflexes
Reye’s Syndrome

Stage III

Continuation of Stage I and II symptoms
Possible coma
Possible cerebral edema
Rarely, respiratory arrest

Stage IV

Deepening coma
Large pupils with minimal response to light
Minimal but still present hepatic dysfunction
Reye’s Syndrome

Stage V

Very rapid onset following stage IV
Deep coma
Seizures
Multiple Organ failure
Flaccidity
Extremely high blood ammonia (above 300 mg/dL of blood)
Death
Reye’s Syndrome

The Centers for Disease Control and Prevention (CDC), the U.S. Surgeon General, the American Academy of Pediatrics (AAP) and the Food and Drug Administration (FDA) recommend that aspirin and combination products containing aspirin not be given to children under 19 years of age during episodes of fever-causing illnesses.
Should you take aspirin if you are pregnant?
Answer: Not recommended, especially after the 32nd week
COX-2 Selective Inhibitors

Celecoxib (Celebrex®)
Meloxicam (Mobic®)
*Rofecoxib (Vioxx®)
*Valdecoxib (Bextra®)

* Removed from market due to high incidence of cardiovascular thrombotic events
COX-2 Selective Inhibitors

Compared to non-selective COX inhibitors these drugs have:

Similar analgesic, antipyretic and antiinflammatory effects
About half of the gastrointestinal effects
Negligible effect on platelet aggregation
Lack of cardioprotective effects
Similar renal toxicity
Higher incidence of cardiovascular thrombotic events
Celecoxib (Celebrex®)

<table>
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<tr>
<th>t 1/2</th>
<th>Elimination by kidney</th>
<th>Antiinflammatory Dose</th>
</tr>
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<tbody>
<tr>
<td>11 hr</td>
<td>27%</td>
<td>100-200 mg bid</td>
</tr>
</tbody>
</table>
Celecoxib (Celebrex®)

- Fewer endoscopic ulcers
- Rashes
- No effect on platelet aggregation in normal doses
- Metabolized by CYP2C9 – interaction with warfarin
Meloxicam (Mobic®)

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<th>$t\frac{1}{2}$ (hours)</th>
<th>Elimination by kidney</th>
<th>Antiinflammatory Dose</th>
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<tbody>
<tr>
<td>20</td>
<td>Undertermined</td>
<td>7.5-15 mg tid</td>
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</table>
Meloxicam (Mobic®)

- Not as selective as Celecoxib
- Fewer GI symptoms than other NSAIDs
- Inhibits synthesis of thromboxane 2 A, but in usual doses does not effect platelet function
Nonselective COX Inhibitors

- Diclofenac (Voltaren®)
- Diflunisal (Dolobid®)
- Ibuprofen (Motrin®)
- Indomethacin (Indocin®)
- Ketorolac (Toradol®)
- Naproxen (Aleve®)
- Piroxicam (Feldene®)
- Sulindac (Clinoril®)
Rheumatoid arthritis is an immunologic disease that causes significant systemic effects which shorten life in addition to the joint disease that reduces mobility and quality of life.

NASIDs offer mainly symptomatic relief, they reduce inflammation and the associated pain and often preserve function, but they have little or no effect on the progression of bone and cartilage destruction!
Disease-Modifying Anti-rheumatic Drugs (DMARD’s)
Disease-Modifying Anti-rheumatic Drugs (DMARD’s)

- Modify the progression of bone and cartilage destruction
- Slow-acting when compared with NSAIDs
- Might take 6 weeks to 6 months for a therapeutic effect
- Both biologically derived and non-biologic agents
Abatacept (Orencia®)

Inhibits the activation of T cells

Intravenous infusions at 0, week 2, week, and monthly thereafter

As mono- or combination therapy for rheumatoid arthritis.

Slightly increased risk of infection.
Azathioprine (Imuran®)

Acts through its major metabolite, 6-thioguanine, which suppresses inosinic acid synthesis, B-cell and T-cell function, immunoglobulin production, and interleukin-2 secretion.

Population that responds is bimodal with rapid and slow metabolizers.

Approved therapy for rheumatoid arthritis but is experimental in many other forms autoimmune diseases.

Toxicity includes bone marrow suppression, GI disturbances and increased risk of infection and also lymphomas.
Chloroquine (Resochin®) and Hydroxychloroquine (Plaquenil®)

Antimalarials – mechanism of action in arthritis is unclear.

Rapidly absorbed, highly protein bound, and blood half lives up to 45 days. Are deposited in melanin-containing tissues such as the eyes.

Approved therapy for rheumatoid arthritis but not considered very effective.

Toxicity includes ocular toxicity, dyspepsia, nausea, vomiting, abdominal pain, rashes and nightmares.
Cyclophosphamide (Cytoxan®)

Metabolized to phosphoramidate mustard, which cross-links DNA to prevent cell replication.

Suppresses T-cell and B-cell function by 30 to 40%.

Active against rheumatoid arthritis when given orally at dosages of 2 mg/kg/d but not when given intravenously.

Regularly used to treat systemic lupus erythematosus, vasculitis, Wegener’s granulomatosis, and other severe rheumatic diseases.
Cyclosporine (Sandimmune®)

Through regulation of gene transcription, inhibits interleukin-1 and interleukin-2 receptor production and secondarily inhibits macrophage-T-cell interaction and T-cell responsiveness.

Absorption is incomplete and erratic. Grapefruit juice increases bioavailability by as much as 62%. Is metabolized by CYP3A and is subject to many drug interactions.

Active against rheumatoid arthritis, retarding appearance of new bony erosions. Might also be useful in SLE, polymyositis and dermatomyositis, Wegener’s granulomatosis, and juvenile chronic arthritis.
Leflunomide (Arava®)

Inhibits T-cell proliferation and production of auto-antibodies by B-cells.

Completely absorbed and has a t1/2 of 19 days.

As effective as methotrexate in treating rheumatoid arthritis, including inhibition of bony damage.

Diarrhea occurs in about 25% of patients. Other adverse effects include mild alopecia, weight gain, increased blood pressure, and rarely leucopenia and thrombocytopenia.

Contraindicated in pregnancy.
Methotrexate (Rheumatrex®)

The DMARD first choice in treating rheumatoid arthritis and is used in 50 – 70% of patients.
Inhibits aminoimidazolecarboxamide ribonucleotide (AICAR) transformylase and thymidylate synthetase, with secondary effects on polymorphonuclear chemotaxis.
Approximately 70% absorbed after oral administration.
Also used to treat juvenile chronic arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, polymyositis, dermatomyositis, Wegener’s granulomatosis, giant cell arteritis, SLE, and vasculitis.
Nausea and mucosal ulcers most common. Hepatotoxicity and acute shortness of breath.
Contraindicated in pregnancy.
Mycophenolic acid (Myfortic®)

Converted to mycophenolic acid which inhibits cytosine monophosphate dehydrogenase and T-cell lymphocyte proliferation. Interferes with leukocyte adhesion to endothelial cells through inhibition of E-selectin.

Effective for the treatment of renal disease due to SLE and might be useful vasculitis and Wegener’s granulomatosis.
Rituximab (Rituxan®)

Chimeric monoclonal antibody that targets CD20 B lymphocytes. Used to treat rheumatoid arthritis refractory to anti-TNF agents. Approved for use in combination with methotrexate.

Given as 2 iv infusions of 1000 mg, separated by 2 weeks, and then repeated every 6-9 months. Glucocorticoids iv 30 minutes before infusion decrease incidence and severity of infusion reactions. About 30% of patients develop rashes.
Sulfasalazine (Azulfidine® or Sulfazine®)

Metabolized to sulfapyridine and 5-aminosalicylic acid. Only 10-20% of oral dose is absorbed.

Effective in rheumatoid arthritis and reduces radiologic disease progression. Also used for juvenile chronic arthritis and in ankylosing spondylitis and its associated uveitis.

Approximate 30% discontinue use because of toxicity which includes nausea, vomiting, headache and rash.
TNF-α-Blocking Agents

Adalimumab (Humira®)
Infliximab (Remicade®)
Etanercept (Embril®)
Structures of TNF-α Antagonists Used in Rheumatoid Arthritis

C_H, constant heavy chain; C_L, constant light chain; Fc, complex immunoglobulin region; V_H, variable heavy chain; V_L, variable light chain. Red regions, human derived; blue regions, mouse derived.
Adalimumab

Complexes with soluble TNF-a and prevents its interaction with p55 and p73 cell surface receptors

Administered sq. t \(\frac{1}{2}\) is 10-20 days

Used to treat rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, plaque psoriasis, and Crohn’s disease.

Increased risk of bacterial and macrophage-dependent infections
Infliximab

Mechanism of action same as adalimumab
Administered i.v. 3-5 mg/kg every 8 weeks

Used to treat rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn’s disease.

Increased risk of bacterial and macrophage-dependent infections
Etanercept

Recombinant fusion protein that binds TNF-α and also inhibits lymphotoxin-α

Administered sq. once or twice weekly

Used to treat rheumatoid arthritis, juvenile chronic arthritis, psoriasis, psoriatic arthritis and, ankylosing spondylitis. Also being used in other rheumatic syndromes such as scleroderma, Wegener’s granulomatosis, giant cell arteritis, and sarcoidosis.

Slight risk of bacterial and macrophage-dependent infections.
Combination Therapy with DMARD’s

Most rheumatologists treat moderately aggressive rheumatoid arthritis with combination therapy.

Combinations of DMARD’s can be designed rationally on the basis of complementary mechanisms of action, non-overlapping pharmacokinetics, and non-overlapping toxicities.
Combination Therapy with DMARD’s

When added to methotrexate background therapy, cyclosporine, chloroquine, hydroxychloroquine, leflunomide, infliximab, adalimumab, rituximab, and etanercept have all shown improved efficacy.

In contrast, azathioprine, auranofin, or sulfasalazine plus methotrexate results in no additional therapeutic benefit.

Other combinations have occasionally been used, including the combination of intramuscular gold with hydroxychloroquine.
Combination Therapy with DMARD’s

While it might be anticipated that combination therapy might result in more toxicity, this is often not the case.

Combination therapy for patients not responding adequately to monotherapy is becoming the rule in the treatment of rheumatoid arthritis.
Glucocorticoid Drugs

Corticosteroids have been used in 60-70% of rheumatoid arthritis patients. Their effects are prompt and dramatic, and they are capable of slowing the appearance of new bone erosions.

Corticosteroids may be administered for certain serious extra-articular manifestations of rheumatoid arthritis such as pericarditis or eye involvement or during periods of exacerbation.

When prednisone is required for long-term therapy, the dosage should not exceed 7.5 mg daily, and gradual reduction of the dose should be encouraged. Alternate-day corticosteroid therapy is usually unsuccessful in rheumatoid arthritis.
Glucocorticoid Drugs

Other rheumatic diseases in which the corticosteroids' potent anti-inflammatory effects may be useful include vasculitis, systemic lupus erythematosi, Wegener's granulomatosis, psoriatic arthritis, giant cell arthritis, sarcoidosis, and gout.

Intra-articular corticosteroids are often helpful to alleviate painful symptoms and, when successful, are preferable to increasing the dosage of systemic medication.
Glucocorticoid Drugs

Prolonged use of these drugs leads to serious and disabling toxic effects.

There is controversy over whether many of these side effects occur at doses below 7.5 mg prednisone equivalent daily, although many experts believe that even 3-5 mg/d can cause these effects in susceptible individuals when this class of drugs is used over prolonged periods.
Acetaminophen (Tylenol®)

Acetaminophen is one of the most important drugs used in the treatment of mild to moderate pain when an anti-inflammatory effect is not necessary. Phenacetin, a prodrug that is metabolized to acetaminophen, is more toxic than its active metabolite and has no rational indications.
Acetaminophen (Tylenol®)

Acetaminophen is the active metabolite of phenacetin and is responsible for its analgesic effect. It is a weak COX-1 and COX-2 inhibitor in peripheral tissues and possesses no significant anti-inflammatory effects.
Acetaminophen (Tylenol®)

Acetaminophen is administered orally. Absorption is related to the rate of gastric emptying, and peak blood concentrations are usually reached in 30-60 minutes. Acetaminophen is slightly bound to plasma proteins and is partially metabolized by hepatic microsomal enzymes and converted to acetaminophen sulfate and glucuronide, which are pharmacologically inactive. Less than 5% is excreted unchanged. A minor but highly active metabolite (N-acetyl-p-benzoquinone) is important in large doses because it is toxic to both liver and kidney. The half-life of acetaminophen is 2-3 hours and is relatively unaffected by renal function. With toxic doses or liver disease, the half-life may be increased twofold or more.
Acetaminophen (Tylenol®)

Acetaminophen alone is inadequate therapy for inflammatory conditions such as rheumatoid arthritis, although it may be used as an analgesic adjunct to anti-inflammatory therapy.

For mild analgesia, acetaminophen is the preferred drug in patients allergic to aspirin or when salicylates are poorly tolerated. It is preferable to aspirin in patients with hemophilia or a history of peptic ulcer and in those in whom bronchospasm is precipitated by aspirin.

Unlike aspirin, acetaminophen does not antagonize the effects of uricosuric agents; it may be used concomitantly with probenecid in the treatment of gout.

It is preferred to aspirin in children with viral infections.
Acetaminophen (Tylenol®)

Adverse Effects

In therapeutic doses, a mild increase in hepatic enzymes may occasionally occur in the absence of jaundice; this is reversible when the drug is withdrawn.

With larger doses, dizziness, excitement and disorientation can be seen. Ingestion of 15 g of acetaminophen may be fatal, death being caused by severe hepatotoxicity with centrilobular necrosis, sometimes associated with acute renal tubular necrosis.

Doses greater than 4-6 g/d are not recommended and a history of alcoholism contraindicates even this dose. Early symptoms of hepatic damage include nausea, vomiting, diarrhea, and abdominal pain.
Acetaminophen (Tylenol®)

Cases of renal damage without hepatic damage have occurred, even after usual doses of acetaminophen. Therapy is much less satisfactory than for aspirin overdose. In addition to supportive therapy, the measure that has proved most useful is the provision of sulfhydryl groups in the form of acetylcysteine to neutralize the toxic metabolites.

Hemolytic anemia and methemoglobinemia are very rare adverse events. Interstitial nephritis and papillary necrosis—serious complications of phenacetin—have not occurred nor has gastrointestinal bleeding. Caution is necessary in patients with any type of liver disease.
Acetaminophen (Tylenol®)

Acute pain and fever may be effectively treated with 325-500 mg four times daily and proportionately less for children.