PATHOGENESIS AND MANAGEMENT OF HYPERURICEMIA AND GOUT

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Primary Hyperuricemia

1. Increased production of uric acid
   - Idiopathic
   - Associated with specific enzyme defects
     - Hypoxanthine-guanine phosphoribosyltransferase
       - Partial or complete deficiency
     - PP-ribose-P synthetase overactivity

2. Decreased renal excretion of uric acid
   - Idiopathic

Secondary Hyperuricemia

1. Increased production of uric acid
   - Associated with increased nucleic acid turnover
     - Myeloproliferative disorders
     - Lymphoproliferative disorders
     - Chronic hemolytic anemias
     - Psoriasis
   - Associated with increased synthesis de novo
     - Glucose-6-phosphatase deficiency
     - 2-ethylamino-1,3,4-thiadiazole
     - Methylene-blue (demonstrated in vitro only)
   - Associated with increased catabolism of nucleotides
     - Fructose ingestion or infusion
     - Exercise

2. Decreased renal excretion of uric acid
   - Reduced renal functional mass
     - Chronic renal disease
   - Decreased fractional excretion of uric acid
     - Lead nephropathy
   - Conditions associated with hyperlactic acidemia
     - Acute ethanol ingestion
     - Toxemia of pregnancy
     - Chronic beryllium disease
   - Conditions associated with increased levels of beta-hydroxybutyrate and acetoacetate
     - Starvation
     - Diabetic Ketoacidosis
   - Glucose-6-phosphatase deficiency
   - Associated with drug administration
     - Pyrazinamide
     - Salicylates (in low dose)
     - Ethambutol
     - Diuretics

Conditions associated with contraction of extracellular fluid volume

- Dehydration
- Salt restriction
- Diabetes insipidis
- Diuretics

Diagnostic Parameters of Gout

Definitive Diagnosis

Demonstration of negatively birefrigent monosodium urate crystals in joint fluid or in a nodule (tophi)

Highly suggestive Triad

- Hyperuricemia (> 7 mg/100 ml in males)
- Acute monoarticular arthritis
- Relief from arthritic symptoms following test course of colchicine (0.5 mg/hr)

Helpful Adjuncts

- Males (over age 40) most often affected
- Distal joint (e.g., big toe) in lower extremity affected
- Onset of acute attacks after stress or trauma
- Exquisite joint pain

Drug Management of Acute Gouty Arthritis

Drug	Route	Dose	Major Adverse Effects	Relative Contraindications
Colchicine	Oral	0.6 mg/hr x 12 doses	Nausea, vomiting, diarrhea, gastric irritation	Active peptic ulcer disease, liver disease, or renal disease
	IV	1-2 mg q6hr (total dose $\leq$ 4 mg)	Leukopenia, local irriation(if infiltrated), sclerosis of veins	Leukopenia, poor veins, recent therapy with large doses of colchicine, liver disease, or renal disease
Indomethacin	Oral	150 mg initially then 50 tid with taper	Gastric irritation, CNS effects	Active or recurrent peptic ulcer disease, psychosis, pregnancy, childhood
Phenylbutazone	Oral	200 mg tid with taper (total therapy < week)	Gastric irritation, bone marrow suppression, salt retention	Blood dyscrasia, congestive heart failure, childhood
Naproxen	Oral	500 mg followed by 250 mg tid with taper	Not established	Not established
ACTH	IM	40 USP units tid x 2-3 days	Glucose intolerance, ? gastric irritation, other effects of steriods	Diabetes, adrenal insufficiency
Triamcinolone (or equivalent glucocorticoid)	Intra-articular	10-40 mg depending on the joint	Crystal-induced synovitis	Septic arthritis, cellulitis over involved joint

Antihyperuricemic Agents

Drug	Route	Dose	Major Adverse Effects	Relative Contraindications
Probenecid	Oral	250-500 mg tid to qid	Gastric irritation Uric acid stones Skin rash	Overproduction of uric acid, uric acid stones, GFR < 50% of normal, salicylate administration
Sulfinpyrazone	Oral	100-200 mg tid to qid	Gastric irritation Uric acid stones Skin rash Bone marrow suppression	Overproduction of uric acid, uric acid stones, GFR, < 50% of normal, salicylate administration Leukopenia
Allopurinol	Oral	300-600 mg qd	Gastric irritation Skin rash Vasculitis Granulomatous hepatitis	Liver disease, bone marrow suppression, administration of cytotoxic agents

METABOLIC EFFECTS OF MAJOR ANTIHYPERURICEMIC AGENTS

Effects of Probenecid on Metabolism of Other Drugs

Decreased renal excretion

Paraaminohippuric acid
Phenolsulfonphthalein
Salicylic acid and its acyl and phenolic glucuronides
Phlorizin and its glucuronide
Acetazolamide
Dapsone and its metabolites
Sulfinpyrazone and its parahydroxy metabolite
Indomethacin
Ampicillin
Penicillin

Reduced volume of distribution

Ampicillin
Ancilin
Nafcilin
Cephaloridine

Impairment of hepatic uptake

Bromsulfonphthalein
Indocyanin green
Rifampicin

Metabolic Effects of Allopurinol

	Clinical Effect	Mechanism	Effector
1.	Hypouricemia	Xanthine oxidase inhibition	Allopurinol Oxipurinol
2.	Decreased total purine production	Inhibition of PP-ribose-P amidotransferase PP-ribose-P depletion	Allopurinol-N-ribosylphosphate IMP Allopurinol
3.	Orotidinuria	Inhibition of orotidine 5'-phosphate decarboxylase	Oxipurinol-7-N-ribosylphosphate Oxipurinol-1-N-ribosylphosphate Allopurinol-1-N-ribosylphosphat
4.	Orotic aciduria	Inhibition of orotate phosphoribosyltransferase PP-ribose-P depletion	? OMP Allopurinol
5.	Prolongation of half-life of drugs metabolized by the microsomal oxidizing system	Inhibition of hepatic microsomal drug-metabolizing enzymes	Unknown
6.	Apparent increased activity of orotate phosphoribosyltransferase and orotidylic decarboxylase	? Stabilization of enzymes to extraction ? Activation	Allopurinol-1-N-ribosylphosphat Unknown

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