

Mesalamine for Inflammatory Bowel Disease

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Outline

- Clinical Case of Ulcerative Colitis
- Mesalamine Pharmacodynamics
- Mesalamine Pharmacokinetics
- Safer Mesalamine Formulations
- Conclusion

The Clinical Case

Clinical Presentation

- 20 year-old woman presents with **bloody diarrhea** and crampy abdominal pain.
- Proctosigmoidoscopy reveals **edematous, friable, ulcerating sigmoid colon** without normal vascular markings.

Normal

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Patient

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Ulcerative Colitis

- **Chronic, relapsing inflammatory bowel disease** primarily presenting in young adults (peak incidence 20-25 y/o female > male)
- **Exact cause unknown** – possibly due to overactive T_{H2} immune response in the large intestine (loss of tolerance to normal flora?)

Pathological Features of UC

- Gross

- Edematous, reddened, friable surface – often visible ulceration
- Isolated islands of regenerating mucosa form pseudopolyps
- Continuous distribution from rectum towards proximal colon

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- Microscopic

- Diffuse, mononuclear inflammatory infiltrate
- Frequent microscopic ulcerations into lamina propria and submucosa, but not extending to deeper layers
- Risk of epithelial dysplasia and adenocarcinoma after many years of chronic disease

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Mesalamine

For Ulcerative Colitis?

- 5-aminosalicylic acid (mesalamine) is effective in rheumatoid arthritis.
- Observation that a mesalamine formulation ameliorates ulcerative colitis in patients with rheumatoid arthritis lead to new indication for the drug.

Chemical diagram of 5-aminosalicylic acid, mesalazine removed for copyright reasons.

Mesalamine

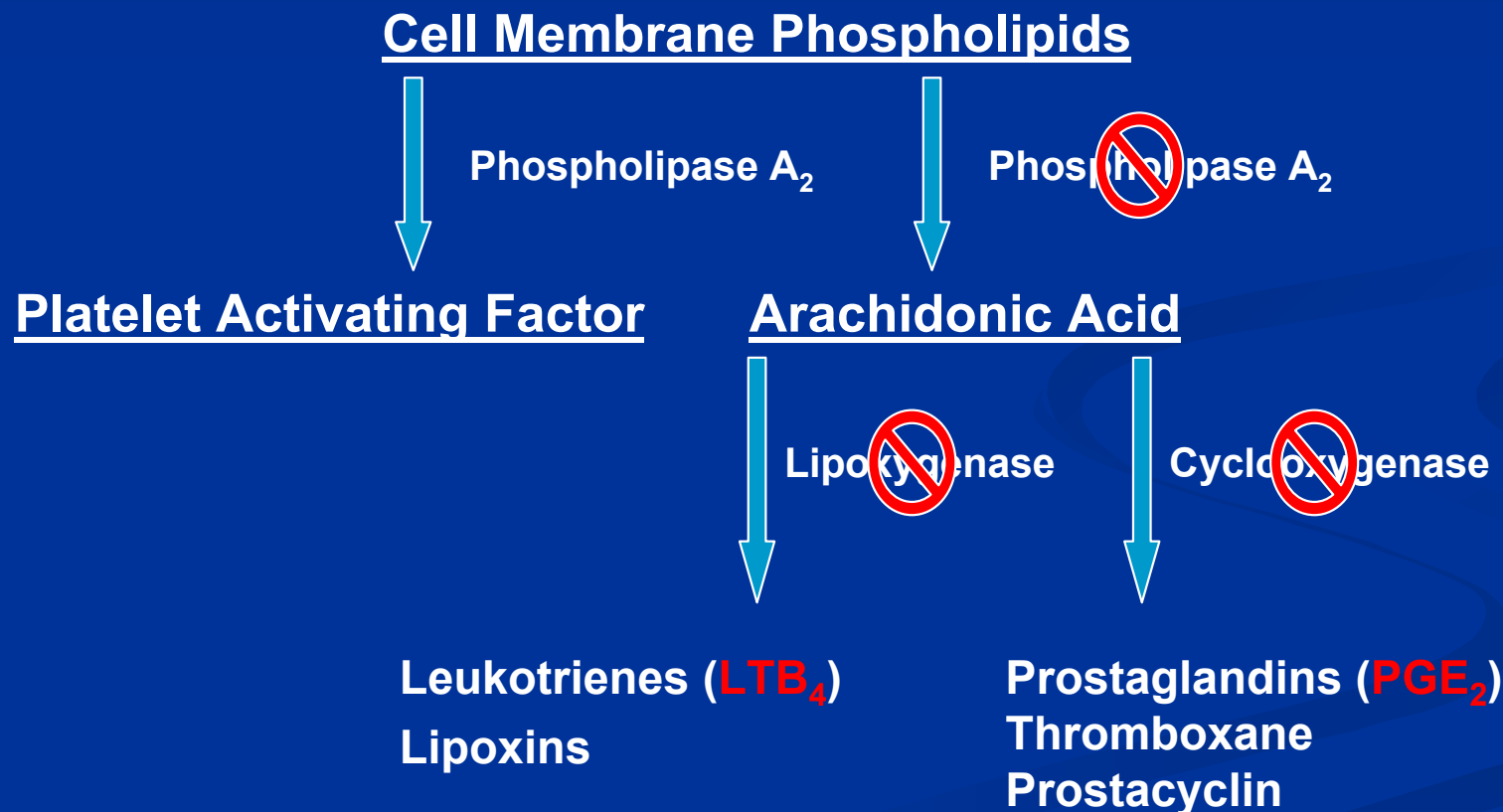
Pharmacodynamics

Diverse Mechanisms of Action

- Mesalamine is *not a product of rational drug design!*
- Therapeutic action of mesalamine is multifactorial:
 - *Antiinflammatory*
 - *Immunosuppressive*

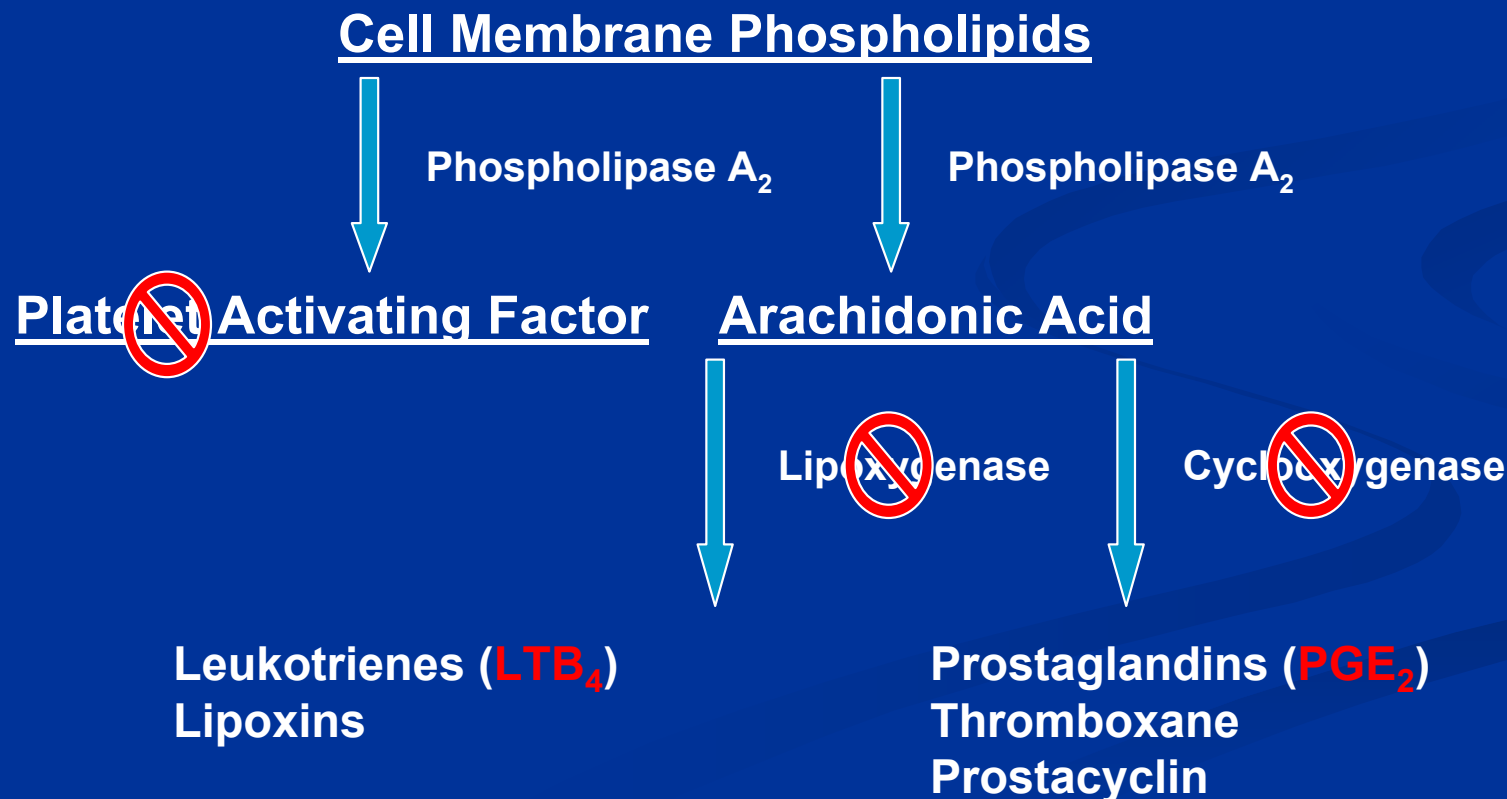
Antiinflammatory Role

- Mesalamine is a salicylate (like aspirin). Suggests influence on synthesis of inflammatory lipid mediators



Antiinflammatory Role

- Mesalamine **inhibits** the enzymatic activity of **Cyclooxygenase**, **Lipoxygenase**, and **PAF** synthesis.



Immunosuppressive Role

- Mesalamine **promotes the release of adenosine**, which impairs leukocyte function and activation.
- Mesalamine interferes with **IL-1, IL-2, TNF- α** synthesis. These cytokines are crucial for the activation and proliferation of cells mediating the inflammatory process.
- Mesalamine **depresses antibody synthesis by plasma cells**, which may limit antibody-mediated disease process.

Mesalamine

Delivery, Metabolism, Excretion

Drug Targeting and Delivery: The problem

- Efficacy of mesalamine depends on achieving a high concentration at disease site.
- Ulcerative Colitis **mainly affects the colon.**
- **Unformulated mesalamine is absorbed in the small intestine (80%)**

Drug Targeting and Delivery: The Prodrug Solution -- Sulfasalazine

- Sulfasalazine is a prodrug containing mesalamine bound to the antibiotic sulfapyridine via an azo bond. The formulation reduces absorption in the small intestine.

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copyright reasons.

In the terminal ileum and colon, coliform bacteria cleave the azo bond using an azoreductase enzyme releasing the therapeutically active metabolite (mesalamine) at the site of inflammation.

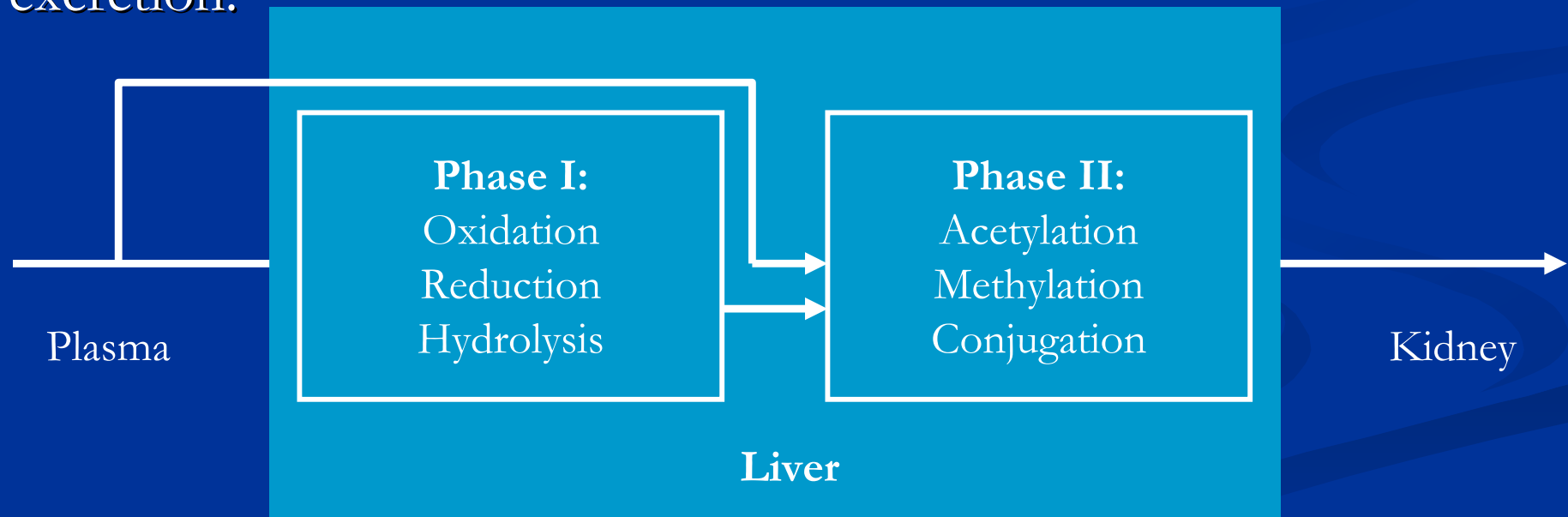
Sulfasalazine

Metabolism and Excretion

- 20% of Sulfasalazine dose is absorbed by the small intestine. Absorbed Sulfasalazine is excreted in bile or urine.
- Mesalamine moiety is generally not absorbed by the large intestine. The small amount that is absorbed is excreted in the urine.
- 60% of Sulfapyridine moiety is absorbed by large intestine, metabolized by liver, and excreted in urine.

Sulfasalazine Toxicity

- Sulfa groups can be **allergenic** causing **rash**, **fever**, and **hepatic dysfunction**.
- Reactions **correlated with sulfa group serum concentrations**. Serum concentration related to hepatic metabolism and renal excretion.



Phase I and II hepatic drug metabolism facilitates drug renal excretion

Slow Acetylator Phenotype

- 50% of caucasians and african-americans have altered hepatic Phase II drug metabolism due to missing isoform of N-acetylation enzyme NAT-2.
- This “slow acetylation” phenotype implies decreased sulfapyridine clearance. So what?

**Pharmacokinetics of
“Slow Acetylator” Phenotype
Chalk-Talk**

Safer Mesalamine Formulations

Mesalimine Dimerization

Sulfapyridine

Mesalamine

Mesalamine

Chemical diagrams removed for
copyright reasons.

Mesalamine

**4-aminobenzoyl- β -
alanine**

Mesalamine

These mesalamine formulations are poorly absorbed by the small intestine and require colonic bacteria for cleavage of the azo bond and release the mesalamine moiety.

Asacol: pH-Dependant Mesalamine Release

Cutaway schematic of large and small intestines removed for copyright reasons.

Asacol is formed by coating mesalamine with pH-sensitive coating. Coating dissolves when pill reaches terminal ileum where the pH is > 7 .

How does Pentasa differ from Asacol

Both Pentasa and Asacol are prescription forms of mesalamine. The difference between Asacol and Pentasa is in the outer chemical coating. Oral Pentasa has a unique formulation. The active ingredient is contained in coated microgranules, which enables a prolonged release of the active substance throughout the intestinal tract, from duodenum to the rectum. Therefore the Pentasa preparation is more useful for Crohn's patients who often have inflammation of the small intestine. The average small bowel transit time is approximately 3-4 hours in healthy volunteers.

Asacol is a delayed release enteric-coated tablets which generally releases the active ingredient only in the colon. While there are always clinical exceptions, Asacol is generally suitable for patients with colitis only (ulcerative colitis or Crohn's colitis), but not disease involving the small intestine.

Pentasa: Sustained Release of Mesalamine

- Pentasa is formed by packaging mesalamine in permeable microgranules.
- Permeable microgranules allow for mesalamine release throughout the intestinal tract.
- Pentasa is more appropriate for Crohn's Disease because of its diffuse intestinal tract distribution.

Diagram removed for copyright reasons.

Conclusion

- **Therapeutic action of Mesalamine is multifactorial:** Antiinflammatory and Immunosuppressive.
- **Delivery to colon is crucial for efficacy:** Accomplished by mesalamine conjugation to make a prodrug (Sulfasalazine and Balsalazine), or by pH-sensitive coating (Asacol).
- **Decrease in drug metabolism and clearance contributes to toxicity:** “Slow Acetylator” phenotype leads to a decrease in sulfapyridine clearance and an increase in its serum concentration. Elevated sulfapyridine serum concentrations increase risk for adverse allergic reactions.