Harvard-MIT Division of Health Sciences and Technology
HST.151: Principles of Pharmocology
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Aminosalicylate for Inflammatory Bowel Disease

Clinical Case of Ulcerative Colitis

- Ulcerative Colitis is as an **idiopathic inflammatory bowel** disease characterized by **preferential ulceration of the colon**. Cancer risk related to recurrences and persistent outbreaks.

Mesalamine Pharmacodynamics

- **Mesalamine** is an **aminosalicylate** with a **multifactorial basis** for its therapeutic efficacy.

- Mesalamine is **anti-inflammatory** because it **inhibits the synthesis** of **inflammatory lipid mediators** (Prostaglandin PE_2, Leukotriene LTB_4, PAF) by **blocking cyclooxygenase** and **lipoxygenase** metabolism of arachidonic acid.

- Mesalamine is **immunosuppressive** because it **blocks synthesis or physiologic action of key inflammatory cytokines** IL-1, IL-2, TNF; these are crucial for inflammatory cell activation and proliferation. Mesalamine also **depresses plasma cell antibody synthesis**.

Mesalamine Pharmacokinetics

- **Unformulated mesalamine** is largely **abosorbed in small intestine**, but the disease site in ulcerative colitis is the colon.

- A **prodrug** is used to deliver mesalamine to the colon. **Sulfasalazine**, the prodrug, consists of **mesalamine conjugated** to the **anti-biotic sulfapyridine** by an **azo bond**. The **azo bond markedly decreases absorption** by small intestinal.

- The **therapeutically effective moiety**, mesalamine, is released from Sulfasalazine in the terminal ileum and colon because **colonic bacteria cleave the azo bond** using the bacterial enzyme **azoreductase**.

- Sulfapyridine moiety is **allergenic** causing a symptomatic triad of **rash**, **fever**, and **hepatic dysfunction**. Adverse reactions are a function of sulfapyridine **serum concentration** (C_{ss}), which is **inversely proportional to drug clearnace** via **hepatic Phase I and II metabolisim** and **renal execretion**.

$$C_{SS} = (\text{Bioavailability} * \text{Dose}) / (\text{Interval}_{\text{Dose}} * \text{Clearance})$$

- 50% of caucasians and african-americans are "**Slow Acetylators**". They have **altered Phase II drug metabolism** due to **missing isoform of N-acetylation enzyme,** NAT-2. Missing isoform **decreases sulfapyridine clearance** and **increases its serum concentration** leading to toxicity.

Alternative Mesalamine Formulations

- Alternative mesalamine formulations focus on **colonic delivery of mesalamine without sulfapyridine conjugation**. For example, **Olsalazine** is formed by **conjugating two mesalamine molecules** via an **azo bond**. Presence of azo bond requires colonic bacteria for cleavage, and ensures colonic mesalamine release.

- **Asacol** packages mesalamine in a pH-sensitive coating. **Coating dissolves only in the colonic setting where pH (~ 7) targeting mesalamine to colon.** This is **crucial for ulcerative colitis** which preferentially affects colon.

- **Pentasa** packages mesalamine in semi-permeable microgranules. Microgranules allow for **slow release of mesalamine throughout intestinal tract**. This **effective for Crohn's Disease** which affects the entire intestinal tract; contrast with Ulcerative Colitis.

****Big Ideas**:** Mesalamine's multifactorial basis for therapeutic efficacy; Prodrug for drug targeting and delivery; Altered drug metabolism phenotype increases risk for toxicity.