

Drugs used in Irritable Bowel Syndrome

- Idiopathic, chronic, relapsing disorder characterized by abdominal discomfort (pain, bloating, distension, or cramps) in association with alterations in bowel habits(diarrhea, constipation, or both).



Drugs used in Irritable Bowel Syndrome

- Antispasmodic or Anticholinergic Agents:

- Dicyclomine

- Hyoscyamine.

- Spasm is not an important symptom in IBS.
- They inhibit muscarinic cholinergic receptors in the enteric plexus and on smooth muscle.
- At usual low doses, have minimal side effects.



Drugs used in Irritable Bowel Syndrome

- Serotonin 5-HT₄- Receptor Agonists:
- Tagaserod:
 - Approved for short term treatment of **women** with IBS who predominantly have constipation.
 - Reduces pain, bloating and hardness of stool.
 - Expensive.



Drugs used in Inflammatory Bowel Disease

- Ulcerative Colitis.
- Crohn's Disease.
 - Unknown etiology.
 - Drugs have different nonspecific antiinflammatory actions.



Drugs used in Inflammatory bowel Disease

- **Aminosalicylates:**
- Used for decades.
- All contain 5-aminosalicylic acid(5-ASA).
- Believed to work topically.
- But, actually, 80% of 5-ASA is absorbed from the small intestine and does not reach the lesions.



Drugs used in Inflammatory Bowel Disease

- Aminosalicylates:

- Azo Compounds:

- Sulfasalazine.

- Balsazide.

- Olsalazine.

- All contain 5-ASA bound by an azo bond (N=N).

- In the intestine, bacteria cleave the bond to release the active 5-ASA.

- Mesalamine Compounds:

- Pentasa: time release 5-ASA formulation.

- Asacol: enteric coated in a pH sensitive resin.

- Rowasa: enema.

- Canasa: suppository.



Drugs used in Inflammatory Bowel Disease

- **Aminosalicylates:**
- **Pharmacodynamics:**
 - Modulate inflammatory mediators derived from both COX and lipooxygenase pathways.
 - Interfere with the production of inflammatory cytokines:
 - Inhibit nuclear factor κ B (NF- κ B).
 - Inhibit cellular functions of natural killer cells, mucosal lymphocytes, and macrophages and may scavenge reactive oxygen metabolites.

Drugs used in Inflammatory Bowel Disease

- **Aminosalicylates:**

- **Clinical Uses:**

- First line drugs for the treatment of mild to moderate active ulcerative colitis.
- Can induce and maintain remission in ulcerative colitis.



Drugs used in Inflammatory Bowel Disease

- **Aminosalicylates:**

- **Adverse Effects:**

- Attributable to systemic absorption: especially in slow acetylators: Nausea, headache, arthralgia, myalgia, bone marrow suppression, and malaise.
- Also, allergic reactions, oligospermia, and folate deficiency.



Drugs used in Inflammatory Bowel Disease

- Glucocorticoids:

- Prednisolone and Prednisone:

- Oral

- Hydrocortisone:

- Enemas, foam or suppositories.

- Budesonide:

- Controlled release oral formulation.

Inhibit production of cytokines(TNF- α , IL-1) and chymokines(IL-8), inflammatory cell adhesion molecules, nitric oxide synthase, phospholipase A₂, Cyclooxygenase-2 and NF-KB.

Drugs used in Inflammatory Bowel Disease

- **Glucocorticoids:**

- **Clinical Uses:**

- Moderate to severe active IBD.

- Prednisolone orally or IV.
- Hydrocortisone, rectally, preferred for rectal and sigmoid involvement.
- Budesonide for ileal and proximal colon involvement.
- Not useful for long term maintenance therapy.



Drugs used in Inflammatory Bowel Disease

- **Antimetabolites:**
- **Azathioprim**
- **6-Mercaotopurine.**
 - Are purine analogs; which produce thioguanine nucleotides.
 - Immunosuppressive.
 - Inhibit purine nucleotide metabolism and DNA synthesis and repair, resulting in inhibition of cell division and proliferation and may promote T-lymphocyte apoptosis.



Drugs used in Inflammatory Bowel Disease

- **Antimetabolites:**
- **Clinical Use:**
 - Onset delayed for 17 weeks.
 - Used in induction and maintenance of remission.
 - Allow dose reduction or elimination of steroids.



Drugs used in Inflammatory Bowel Disease

- **Antimetabolites:**


- **Adverse Effects:**

- Nausea, vomiting, bone marrow suppression, hepatic toxicity and allergic reactions(fever, rash, pancreatitis, diarrhea and hepatitis).
- Allopurinol increases levels of the drugs.




Drugs used in Inflammatory Bowel Disease

- **Methotrexate:**

- Antimetabolite.
 - Can be given orally, subcutaneously and intramuscularly.
 - Works by inhibiting dihydrofolate reductase (DHFRase) enzyme which is important in the synthesis of thymidine and purines.
 - At high doses it inhibits cellular proliferation.
 - At low doses used in IBD, it interferes with the inflammatory actions of interleukin-1, stimulates adenosine release, apoptosis and death of activated T lymphocytes.
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Drugs used in Inflammatory Bowel Disease

- **Methotrexate:**
 - Used in cancer chemotherapy, rheumatoid arthritis and psoriasis.
 - Used for induction and maintenance of remissions of Crohn's Disease.
 - At high doses, can cause bone marrow depression, megaloblastic anemia, alopecia and mucositis.
 - Renal insufficiency may increase risk of hepatic accumulation and toxicity.
 - Side effects counteracted by folate supplementation.
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Drugs used in Inflammatory Bowel Disease


- **Anti-Tumor Necrosis Factor:**
- TNF- α is a key proinflammatory cytokine in the TH1 response in IBD.
- **Infliximab “Remicade”:**
 - Is a chimeric mouse-human monoclonal antibody to human TNF- α .
 - Given IV.
- **Adalimumab:**
 - Fully humanized IgG antibody, given SC.
- **Certolizumab:**
 - Polyethylene glycol Fab fragment of humanized anti- TNF- α , also given SC.

Nomenclature of Monoclonal Antibodies

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|---------------------|---------------------------------------|
| -mab | monoclonal antibody |
| - mo -mab | mouse mab |
| - xi -mab | chimeric mab |
| - zu -mab | humanized mab |
| - mu -mab | human mab |
| - tu -xx-mab | tumor-directed xx mab |
| - li -xx-mab | immune-directed xx mab |
| - ci -xx-mab | cardiovascular-directed xx mab |
| - vi -xx-mab | virus-directed xx mab |

Drugs used in Inflammatory Bowel Disease

Anti-Tumor Necrosis Factor:

- Half life 8-10 days with persistence of antibodies in plasma for 8-12 weeks.
 - Binds to cell surface as well as to membrane-bound TNF- α receptors, preventing the cytokine from binding to its receptors.
 - The Fc portion of human IgG₁ region promotes complement activation and antibody-mediated apoptosis and cellular cytotoxicity of activated lymphocytes and macrophages.
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Drugs used in Inflammatory Bowel Disease

- **Anti-Tumor Necrosis Factor:**

- Used in acute and chronic treatment of patients with moderate to severe IBD.
- Given in repeated doses at 0, 2, and 6 weeks for induction.
- If response is adequate, infusions are repeated every 8 weeks.
- Response might be lost due to development of antibodies to infliximab.



Drugs used in Inflammatory Bowel Disease

• Anti-Tumor Necrosis Factor:

— Serious Adverse effects:

- Infection due to immunosuppression, occur in 6% of patients on infliximab, e.g. reactivation of TB or dissemination, pneumonia, sepsis, pneumocystis, listeriosis, and reactivation of hepatitis B.
- Antibody formation against the murine epitope of infliximab develops in 1/3rd of patients leading to loss of response or infusion reactions.



Drugs used in Inflammatory Bowel Disease

- **Anti-Tumor Necrosis Factor:**
- **Acute Infusion Reactions:** fever, headache, dizziness, urticaria, chest pain, and dyspnea, hypotension, shortness of breath, muscle spasm and chest discomfort.
- **Delayed Reactions or Serum Sickness-like Reactions:** occur after retreatment with infliximab include myalgia, arthralgia, jaw tightness, fever, rash, urticaria, and edema.



Drugs used in Inflammatory Bowel Disease

- **Anti-Tumor Necrosis Factor:**

- **Other Adverse Reactions:** Positive antinuclear antibodies, anti-double stranded DNA, Lupus-like syndrome, severe hepatic reactions, lymphoma, multiple sclerosis and congestive heart failure.

