Chapter-15

Antiamoebic Agents

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ABSTRACT

Antiamoebic agents are a class of drugs used to treat infections caused by amoebae, primarily *Entamoeba histolytica*, the causative agent of amoebiasis. These infections can range from asymptomatic colonization to severe invasive diseases, including amoebic dysentery and liver abscess. The main classes of antiamoebic drugs include luminal agents, systemic agents, and mixed agents, which target different stages of the parasite's lifecycle. Luminal agents like paromomycin and iodoquinol act within the intestinal lumen to eliminate cysts and trophozoites. Systemic agents such as metronidazole and tinidazole penetrate tissues to treat invasive infections. Mixed agents, like nitazoxanide, are effective in both the intestinal lumen and tissues. Metronidazole, the most commonly used antiamoebic, disrupts DNA synthesis in anaerobic organisms. These agents are often used in combination to ensure complete eradication of the parasite, especially in cases of invasive disease. Effective treatment is crucial to prevent complications and transmission. Despite their efficacy, the emergence of drug resistance and adverse effects remain challenges, necessitating ongoing research and development of new antiamoebic therapies.

Introduction to Antiamoebic Agents

Amoebiasis is an infection caused by the protozoan parasite *Entamoeba histolytica*, which primarily affects the intestines and can lead to severe dysentery, colitis, and extraintestinal manifestations such as liver abscesses. Antiamoebic agents are medications designed to treat these infections by targeting different stages of the amoeba's lifecycle, including cysts and trophozoites in the intestinal lumen and tissues. Effective treatment of amoebiasis is crucial to alleviate symptoms, prevent complications, and stop the spread of the parasite.

Classification of Antiamoebic Agents

Antiamoebic agents can be classified based on their site of action and the stage of the parasite they target. The main classes include:

1. Luminal Agents
2. Systemic Agents
3. Mixed Agents

1. **Luminal Agents**

   Examples: Paromomycin, Iodoquinol, Diloxanide Furoate

   Mechanism of Action: Luminal agents act within the intestinal lumen to eliminate both cysts and trophozoites of *Entamoeba histolytica*. They are not absorbed significantly from the gastrointestinal tract, which limits their action to the lumen.

   Therapeutic Use: These agents are primarily used to treat asymptomatic carriers and to prevent relapse after treatment of invasive amoebiasis with systemic agents.

   Adverse Effects: Paromomycin can cause gastrointestinal disturbances, while iodoquinol can lead to neurotoxicity and optic neuritis with prolonged use.

2. **Systemic Agents**

   Examples: Metronidazole, Tinidazole, Chloroquine, Dehydroemetine

   Mechanism of Action: Systemic agents are absorbed into the bloodstream and distributed throughout the body, allowing them to target invasive amoebic infections in tissues, such as liver abscesses and colitis. Metronidazole and tinidazole disrupt DNA synthesis in anaerobic organisms by producing reactive nitrogen species.

   Therapeutic Use: These agents are used to treat invasive amoebiasis, including amoebic liver abscess and severe intestinal infections.

   Adverse Effects: Metronidazole and tinidazole can cause gastrointestinal disturbances, metallic taste, headache, and rarely, neurotoxicity. Alcohol should be avoided during treatment due to the risk of a disulfiram-like reaction.

3. **Mixed Agents**

   Examples: Nitazoxanide, Secnidazole, Ornidazole

   Mechanism of Action: Mixed agents are effective against both luminal and tissue stages of the parasite. Nitazoxanide interferes with the pyruvate-ferredoxin oxidoreductase enzyme-dependent electron transfer reaction, essential for anaerobic energy metabolism.

   Therapeutic Use: These agents are used for both symptomatic intestinal infections and tissue infections, offering a broader spectrum of action.

   Adverse Effects: Generally well-tolerated, but can cause gastrointestinal disturbances and, rarely, allergic reactions.

Specific Agents in Detail

1. **Metronidazole**

   - **Mechanism of Action:** Disrupts DNA synthesis by producing toxic metabolites in anaerobic conditions.
   - **Therapeutic Use:** First-line treatment for invasive amoebiasis, including amoebic liver abscess.
   - **Adverse Effects:** Nausea, vomiting, metallic taste, headache, and potential neurotoxicity.

2. **Paromomycin**
    - **Mechanism of Action:** Binds to the 30S ribosomal subunit, inhibiting protein synthesis in the parasite.
    - **Therapeutic Use:** Effective luminal agent for asymptomatic carriers and post-systemic treatment to prevent relapse.
    - **Adverse Effects:** Gastrointestinal disturbances.

3. **Iodoquinol**
    - **Mechanism of Action:** Exact mechanism is unclear, but it is effective in the intestinal lumen.
    - **Therapeutic Use:** Used for luminal infections.
    - **Adverse Effects:** Neurotoxicity, optic neuritis with prolonged use.

4. **Nitazoxanide**
    - **Mechanism of Action:** Inhibits pyruvate-ferredoxin oxidoreductase enzyme-dependent electron transfer.
    - **Therapeutic Use:** Effective against both luminal and tissue stages.
    - **Adverse Effects:** Generally mild gastrointestinal symptoms.

Metronidazole

Metronidazole is an antimicrobial agent with a broad spectrum of activity, primarily against anaerobic bacteria and some protozoa. Here are key aspects of the pharmacology of metronidazole:

1. **Mechanism of Action:** Metronidazole exerts its antimicrobial effects through a multi-step process involving reduction and formation of cytotoxic products. The drug is taken up by susceptible organisms and undergoes chemical reduction by intracellular electron transport proteins. This reduction process leads to the formation of reactive intermediates that disrupt DNA structure, leading to inhibition of nucleic acid synthesis and DNA strand breakage. This mechanism is particularly effective against anaerobic microorganisms that lack protective enzymes against reactive oxygen species.

2. **Spectrum of Activity:** Metronidazole is effective against a wide range of anaerobic bacteria, including Bacteroides, Clostridium, Fusobacterium, and Peptostreptococcus species. It is also active against certain protozoa, especially Entamoeba histolytica, Giardia lamblia, and Trichomonas vaginalis.

3. **Absorption and Distribution:** Metronidazole is well absorbed from the gastrointestinal tract. It achieves good tissue penetration, including the central nervous system (CNS) and various body fluids. The drug crosses the blood-brain barrier, making it effective for treating anaerobic infections in the CNS.

4. **Metabolism and Elimination:** Metronidazole undergoes extensive metabolism in the liver, and its metabolites are excreted in the urine. The elimination half-life is relatively

short, typically around 8 hours, but may be prolonged in patients with hepatic dysfunction.

5. **Clinical Uses**
    - Metronidazole is used in the treatment of various infections, including:
    - Anaerobic bacterial infections, such as intra-abdominal infections, skin and soft tissue infections, and bacterial vaginosis.
    - Protozoal infections, including amoebiasis, giardiasis, and trichomoniasis.
    - Helicobacter pylori eradication in combination with other antibiotics for peptic ulcer disease.

6. **Adverse Effects:** Common side effects include nausea, vomiting, metallic taste, and gastrointestinal upset. Neurological side effects, such as peripheral neuropathy and seizures, are rare but can occur with prolonged use or high doses.

7. **Drug Interactions:** Metronidazole can interact with certain drugs, including disulfiram (causing a disulfiram-like reaction), warfarin (potentiating anticoagulant effects), and alcohol (leading to a disulfiram-like reaction).

8. **Precautions and Contraindications:** Metronidazole should be used with caution in patients with hepatic impairment. It is contraindicated in the first trimester of pregnancy due to potential teratogenic effects

Tinidazole

Tinidazole is an antiprotozoal and antibacterial medication with a structure similar to metronidazole. It shares some similarities in its mechanism of action and spectrum of activity with metronidazole but has certain pharmacokinetic differences. Here is an overview of the pharmacology of tinidazole:

1. **Mechanism of Action:** Tinidazole, like metronidazole, is a 5-nitroimidazole derivative. Its antimicrobial activity is based on the reduction of its nitro group by intracellular transport proteins within microorganisms. The reduced intermediates formed disrupt the DNA structure of the microorganisms, leading to inhibition of nucleic acid synthesis and eventual cell death.

2. **Spectrum of Activity:** Tinidazole has a broad spectrum of activity against anaerobic bacteria and protozoa. It is effective against various pathogens, including Trichomonas vaginalis (causing trichomoniasis), Giardia lamblia (causing giardiasis), and Entamoeba histolytica (causing amoebiasis). Tinidazole is also active against certain anaerobic bacteria, similar to metronidazole.

3. **Absorption and Distribution:** Tinidazole is well absorbed after oral administration, and its absorption is not significantly affected by food. It has good tissue penetration, and therapeutic concentrations are achieved in various body tissues and fluids, including the gastrointestinal tract.

4. **Metabolism and Elimination:** Tinidazole undergoes hepatic metabolism, primarily through conjugation, and its metabolites are excreted in the urine. The elimination half-life is approximately 12-14 hours.

5. **Clinical Uses:** Tinidazole is used in the treatment of various infections, including:
    - **Trichomoniasis:** A sexually transmitted infection caused by Trichomonas vaginalis.
    - **Giardiasis:** An intestinal infection caused by Giardia lamblia.
    - **Amoebiasis:** An infection caused by Entamoeba histolytica.
    - **Bacterial vaginosis:** An overgrowth of harmful bacteria in the vagina.

6. **Adverse Effects:** Common side effects of tinidazole include nausea, metallic taste, and gastrointestinal upset. Neurological side effects are rare but can occur, including headache and dizziness. Like metronidazole, the concurrent use of alcohol should be avoided due to the potential for a disulfiram-like reaction.

7. **Precautions and Contraindications:** Tinidazole should be used with caution in patients with hepatic impairment. It is contraindicated in the first trimester of pregnancy, similar to metronidazole.

Paromomycin

Paromomycin is an aminoglycoside antibiotic with activity against various parasites, including certain protozoa and helminths. Here is an overview of the pharmacology of paromomycin:

1. **Mechanism of Action:** Paromomycin's primary mechanism of action involves binding to the 30S ribosomal subunit of the parasite's ribosome. By interfering with protein synthesis, it disrupts the translation of mRNA, leading to inhibition of protein production. This ultimately results in the death of the parasite.

2. **Spectrum of Activity:** Paromomycin is effective against a variety of parasites, including:
    - **Entamoeba histolytica:** The causative agent of amoebiasis.
    - **Giardia lamblia:** A protozoan causing giardiasis.
    - **Cryptosporidium parvum:** An intestinal parasite causing cryptosporidiosis.
    - **Leishmania species**: Parasites causing leishmaniasis.

3. **Absorption and Distribution:** Paromomycin is poorly absorbed from the gastrointestinal tract when administered orally. Therefore, it is generally administered orally for the treatment of intestinal infections. When used to treat systemic infections, it may be administered intravenously.

4. **Metabolism and Elimination:** Paromomycin is not significantly metabolized in the body. It is excreted primarily unchanged in the feces after oral administration. In cases where intravenous administration is used, it is excreted mainly in the urine.

5. **Clinical Uses:** Paromomycin is used in the treatment of various parasitic infections, including:
    - **Amoebiasis:** Intestinal infection caused by Entamoeba histolytica.
    - **Giardiasis:** Infection of the small intestine caused by Giardia lamblia.
    - **Cryptosporidiosis:** Infection of the gastrointestinal tract caused by Cryptosporidium parvum.
    - **Leishmaniasis:** A group of infections caused by various species of the Leishmania parasite.

6. **Adverse Effects:** Common side effects of paromomycin include gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Since it is not significantly absorbed from the gastrointestinal tract, systemic side effects are generally minimal compared to other aminoglycosides.

7. **Precautions and Contraindications:** Paromomycin should be used with caution in individuals with renal impairment. It is contraindicated in patients with a known hypersensitivity to aminoglycosides.

Diloxanide Furoate

Diloxanide furoate is an antiprotozoal medication used in the treatment of intestinal infections, particularly those caused by the amoeba Entamoeba histolytica. Here is an overview of the pharmacology of diloxanide furoate:

1. **Mechanism of Action:** Diloxanide furoate exerts its antiprotozoal effects by inhibiting the growth and multiplication of Entamoeba histolytica in the intestinal lumen. While the exact mechanism of action is not fully understood, it is believed that diloxanide furoate is metabolized to its active form, diloxanide, in the intestines. Diloxanide then acts locally, preventing the amoeba from dividing and causing damage to the intestinal tissues.

2. **Absorption and Distribution:** Diloxanide furoate is administered orally and is poorly absorbed from the gastrointestinal tract. The drug remains largely in the intestinal lumen, where it exerts its therapeutic effects against the amoeba. Due to its poor absorption, systemic distribution is minimal.

3. **Metabolism and Elimination:** Diloxanide furoate is metabolized in the intestinal mucosa to its active form, diloxanide. The majority of the drug is excreted in the feces, primarily as unchanged diloxanide.

4. **Clinical Uses:** Diloxanide furoate is used in the treatment of asymptomatic cyst passers or individuals with mild intestinal amoebiasis caused by Entamoeba histolytica. It is often used in combination with tissue amoebicides, such as metronidazole, which act on the invasive forms of the amoeba in tissues.

5. **Adverse Effects:** Diloxanide furoate is generally well-tolerated. Common side effects are mild and may include gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Allergic reactions are rare.

6. **Precautions and Contraindications:** Diloxanide furoate is contraindicated in patients with known hypersensitivity to the drug. It is generally considered safe for use during pregnancy and lactation, but as with any medication, the potential benefits and risks should be carefully evaluated.

7. **Dosage and Administration:** The dosage of diloxanide furoate is typically determined based on the severity of the infection and the individual's weight. The medication is usually administered orally.

Iodoquinol

Iodoquinol is an antiprotozoal medication used in the treatment of certain intestinal parasitic infections. Here's an overview of the pharmacology of iodoquinol:

1. **Mechanism of Action:** The exact mechanism of action of iodoquinol is not fully understood. However, it is believed to act by interfering with the energy metabolism of the parasites, leading to their death. Iodoquinol is particularly effective against certain protozoa and is used in the treatment of infections such as amoebiasis.

2. **Absorption and Distribution:** Iodoquinol is poorly absorbed from the gastrointestinal tract after oral administration. Most of the drug remains in the intestinal lumen, where it exerts its therapeutic effects against the parasites. Due to its poor absorption, systemic distribution is limited.

3. **Metabolism and Elimination:** Iodoquinol undergoes some degree of metabolism in the liver. The majority of the drug and its metabolites are excreted in the feces. A small portion may be excreted in the urine.

4. **Clinical Uses:** Iodoquinol is primarily used in the treatment of intestinal infections caused by Entamoeba histolytica, a protozoan parasite that can cause amoebiasis. It is effective against the luminal forms of the parasite in the intestines. However, iodoquinol is generally not used as a first-line treatment for invasive amoebiasis; tissue amoebicides such as metronidazole are often preferred for such cases.

5. **Adverse Effects:** Common side effects of iodoquinol include gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Neurological side effects are rare but have been reported, particularly with prolonged use or high doses. Neurotoxicity may manifest as peripheral neuropathy, optic neuropathy, or other neurological symptoms.

6. **Precautions and Contraindications:** Iodoquinol should be used with caution in individuals with a history of neurological disorders. It is contraindicated in patients with optic neuropathy or hypersensitivity to the drug.

7. **Dosage and Administration:** The dosage of iodoquinol is typically determined based on the specific infection being treated and the patient's weight. It is usually administered orally.

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Metronidazole + Diloxanide Furoate

Metronidazole and diloxanide furoate are often prescribed in combination for the treatment of amoebic infections, particularly amoebiasis caused by the protozoan parasite Entamoeba histolytica. Here's an overview of the pharmacology of this combination:

Metronidazole

1. **Mechanism of Action**
   - Metronidazole is a 5-nitroimidazole derivative.
   - It enters the microbial cell, is reduced by intracellular electron transport proteins, and generates cytotoxic intermediates.
   - These intermediates disrupt DNA structure, leading to inhibition of nucleic acid synthesis and DNA strand breakage.
2. **Spectrum of Activity**
   - Metronidazole is effective against anaerobic bacteria and certain protozoa, including Entamoeba histolytica.
   - It is widely used for various infections, including amoebiasis, bacterial vaginosis, and certain anaerobic bacterial infections.
3. **Absorption and Distribution**
   - Metronidazole is well absorbed from the gastrointestinal tract.
   - It achieves good tissue penetration, including the central nervous system (CNS).
4. **Metabolism and Elimination**
   - Metronidazole undergoes hepatic metabolism, and its metabolites are excreted in the urine.
   - The elimination half-life is relatively short, around 8 hours.

Diloxanide Furoate

1. **Mechanism of Action**
   - Diloxanide furoate inhibits the growth and multiplication of Entamoeba histolytica in the intestinal lumen.
   - The active form, diloxanide, acts locally to prevent the amoeba from dividing and causing damage to the intestinal tissues.
2. **Absorption and Distribution**
   - Diloxanide furoate is poorly absorbed from the gastrointestinal tract.
   - It remains largely in the intestinal lumen, exerting its effects against the amoeba locally.

3. Metabolism and Elimination

- Diloxanide furoate is metabolized in the intestinal mucosa to its active form, diloxanide.
- The majority of the drug is excreted in the feces, primarily as unchanged diloxanide.

Combination Therapy

1. Rationale

- Combining metronidazole with diloxanide furoate is often done to target both the invasive and luminal forms of Entamoeba histolytica.
- Metronidazole acts systemically to target the amoeba in tissues, while diloxanide furoate acts locally in the intestinal lumen.

2. Clinical Uses

- This combination is used in the treatment of amoebiasis to ensure a more comprehensive and effective eradication of the parasite.

3. Adverse Effects

- Adverse effects are generally those associated with each individual drug, including gastrointestinal symptoms, metallic taste, and potential neurological side effects with metronidazole.

4. Precautions and Monitoring

- The combination should be used under the guidance of a healthcare professional.
- Monitoring for adverse effects, especially with metronidazole, is important during the course of treatment.