Amebicidal Drugs

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Amebiasis is an infection of the colon caused by Entamoeba histolytica. Infection occurs by ingestion of water and food contaminated with feces (containing cysts of Entamoeba histolytica). In this article, we will study in detail the various amebicides, their mechanism of action, adverse effects/toxicity, contraindications, drug interactions and drugs of choice. Other important therapeutic aspects of individual drugs will also be studied.

Overview of Amebiasis

Amebiasis is an infection of the intestine caused by Entamoeba histolytica. It is a protozoan parasite. Human beings and other non-human primates are the main hosts. Infection occurs by ingestion of water and food contaminated with feces. The contaminated food/water contains the cysts of Entamoeba histolytica. It can cause extra-intestinal invasive infections.

E. dispar and E. histolytica are the only pathogenic amoebas known to humans. The protozoan enters the digestive tract and multiplies in the terminal ileum or colon to the trophozoite stage. Trophozoite of E. Histolytica is a motile form.

Inside the intestine, it causes necrosis and perforation of the intestinal wall. It can also penetrate the intestinal wall and reach the liver via the portal vein, where it may cause a fatal liver abscess.
Cysts are excreted into the feces. The life cycle of E. histolytica is completed at this stage. It can survive in the environment for weeks to months. Factors that increase the chances of amebiasis are travel to an endemic area, consumption of contaminated food/water and anal intercourse. The infection can cause an asymptomatic disease to mild to moderate intestinal cases (ulcers, dysentery) to severe or chronic cases.

Amebiasis is prevalent highly in developing countries where general sanitation hygiene is not available.

The classic symptoms of amebiasis are bloody or watery diarrhea, fever (10—30 % patients), anorexia, and weight loss. Rectal bleeding can occur without diarrhea in children. It remains asymptomatic in most individuals and resolves on its own. Invasive infections result when E. histolytica reaches organs such as the liver via the systemic circulation. If the infection is limited to the intestine it is called non-invasive infection.

Treatment is therefore directed at disinfecting luminal trophozoites (non-invasive infection), as well as those in the tissue (invasive infection) if the infection has spread to that extent. Not all drugs can disinfect the cysts of E. histolytica. Drugs are usually active either in the tissues or in the intestinal lumen, thereby necessitating a combination therapy for symptomatic amebiasis.

Patients should be educated to avoid contaminated food/water or undercooked food.

Functional and Chemical Classification of Amebicides

Tissue amebicides

- Nitro-imidazoles: Metronidazole, Tinidazole, etc.
- Alkaloid derivatives: Emetine and Dehydroemetine

Luminal amebicides

- Amide: Diloxanide furoate, Nitazoxanide
- 8-Hydroxyquinolines: Iodoquinol
- Antibiotics: Tetracycline and Erythromycin

Amebicidal Drugs

Tissue amebicides

Metronidazole

- A nitro-imidazole
- Selectively toxic to anaerobic microorganisms
- Half-life of metronidazole is 7.5 hours.

<table>
<thead>
<tr>
<th>Mechanism of action</th>
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<tbody>
<tr>
<td>The nitro-group of nitro-imidazoles undergoes bioactivation by ferredoxin (which is present only in anaerobic microorganisms) to form reactive toxic metabolites (nitro radicals) that inhibit nucleic acid synthesis. This occurs by nitro-radicals competing with the energy metabolism pathway of anaerobic microorganisms.</td>
</tr>
</tbody>
</table>
Clinical uses

- **Amebiasis**: drug of choice. It kills the tissue and intestinal trophozoites; however, it is not effective against cysts of *E. histolytica*.
  - also indicated for an invasive type of amebiasis
  - **Giardiasis**: drug of choice
  - **Trichomoniasis**: drug of choice (a single dose of 2 g)

- **Pseudomembranous colitis** (caused by *Clostridium difficile*): drug of choice
  - Effective against *Helicobacter pylori*. However, this should only be used in combination with another antibiotic (e.g., amoxicillin) and a proton pump inhibitor (e.g., omeprazole).
  - Effective as treatment or prophylaxis of peri- and post-operative anaerobic infections (usually in combination with cephalosporins for a broad-spectrum coverage).

- **Acute necrotizing ulcerative gingivitis** (ANUG): drug of choice (in combination with amoxycillin, tetracycline, or erythromycin)

Adverse effect/toxicity

- Nausea, vomiting, abdominal cramps, metallic taste, oral moniliasis, headache, dark urine
  - Rare: neurotoxicity; if occurs, the drug should be discontinued.
  - Resistance to nitro-imidazoles develops when the microorganisms become deficient in the pathway that generates nitro-radicals.

Drug interactions

- Alcohol should not be used during metronidazole therapy because a disulfiram-like reaction can occur.
  - Cimetidine can reduce metronidazole metabolism. If administered together, dose adjustment is required.
  - Metronidazole reduces warfarin metabolism.
  - Metronidazole decreases renal excretion of lithium.

Contraindications

- Blood dyscrasias
- Neurological disease
- Chronic alcoholism
  - Not contraindicated in pregnancy, but should be used with caution.

Tinidazole

Tinidazole is a second-generation nitro-imidazole. Its efficacy equals that of metronidazole, but it has a shorter course of treatment (3 days vs. 10 days for metronidazole), has a longer half-life (12—14 hours), and is more expensive.

- **Amebic dysentery**
  - Approved by US FDA only for diarrhea caused by *Cryptosporidium* and *Giardia intestinalis*.
  - Shown to be effective against many other organisms such as *Ascaris, Trichomonas vaginalis, tapeworms, several helminthic infections*, etc.

- **Acute necrotizing ulcerative gingivitis** (ANUG): drug of choice (in combination with amoxycillin, tetracycline, or erythromycin)

Other nitro-imidazoles

- Secnidazole, ornidazole, and satranidazole
- They are similar to metronidazole/tinidazole but with a longer half-life.
- Satranidazole has much better tolerability (lower side effects).

Nitazoxanide

Nitazoxanide is a new nitrothiazole antiparasitic drug and Prodrug – gets converted to tizoxanide. Effective against numerous intestinal protozoa and helminths

Mechanism of action

Inhibits pyruvate: ferredoxin oxidoreductase enzyme (PFOR), which is essential for electron transport energy metabolism in anaerobic organisms.

Clinical uses

- **Amebic dysentery**
  - Approved by US FDA only for diarrhea caused by *Cryptosporidium* and *Giardia intestinalis*.
  - Shown to be effective against many other organisms such as *Ascaris, Trichomonas vaginalis, tapeworms, several helminthic infections*, etc.

Adverse effect/toxicity

- GI symptoms such as abdominal pain, nausea, vomiting, and diarrhea (dose-dependent)
  - Usually extremely well tolerated.

Drug interactions

- None documented. However, the active metabolite tizoxanide is highly protein-bound. Therefore, its use with other highly protein-bound drugs must be avoided or done with caution.

Emetine & Dehydroemetine

Because of toxicity concerns rarely used. For example, severe amebiasis when metronidazole cannot be used. These act only against the trophozoites but not against the cysts.
In the setting of severe amebiasis, these drugs should be administered s.c. or i.m. (and not i.v.) for at least 3—5 days.

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Block ribosomal movement along mRNA</th>
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<tbody>
<tr>
<td>\textbf{Adverse effect/toxicity}</td>
<td>\begin{itemize} \item Dose/time-dependent \item GI symptoms: nausea, vomiting, diarrhea \item Pain and tenderness at the injection site; muscle weakness; minor ECG changes \item Severe effects involve cardiotoxicity, e.g., arrhythmias. \item Dehydroemetine is somewhat better tolerated than emetine. \end{itemize}</td>
</tr>
<tr>
<td>\textbf{Contraindications}</td>
<td>\begin{itemize} \item Absolute: cardiac disease and renal disease \item Relative: younger children and pregnant women \end{itemize}</td>
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\section*{Luminal amebicides}

\textbf{Diloxanide furoate}
\begin{itemize} \item Amide \item Directly kills luminal trophozoites \item It does not kill the tissue trophozoites. \item No antibacterial action \item Prodrug (releases free diloxanide as the active metabolite) \end{itemize}

\begin{tabular}{|c|l|}
\hline
\textbf{Mechanism of action} & Unknown \\
\hline
\textbf{Clinical uses} & \begin{itemize} \item Asymptomatic intestinal infection (alone). \item Amebic colitis (in conjunction with a nitro-imidazole; can be used alone in very mild cases) \item Less effective in invasive dysentery, because of poor tissue amebicidal action \item Although one course is usually sufficient, some chronic cases may require repeat courses for eradication. \item Please note diloxanide furoate is not available in the USA. \end{itemize} \\
\hline
\textbf{Adverse effect/toxicity} & \begin{itemize} \item Usually well tolerated \item Flatulence, nausea, itching \item Rare: urticaria \end{itemize} \\
\hline
\textbf{Drug interactions} & No known interactions \\
\hline
\end{tabular}

\textbf{Iodoquino1}

Directly kills amebic trophozoites, thereby inhibiting cyst production. Ineffective as tissue amebicide.

\begin{tabular}{|c|l|}
\hline
\textbf{Mechanism of action} & Unknown \\
\hline
\textbf{Clinical uses} & \begin{itemize} \item Asymptomatic intestinal infection (alone) \item Amebic colitis (in conjunction with a nitro-imidazole; can be used alone in very mild cases) \item Giardiasis \item Local treatment of monilial and trichomonas vaginitis \end{itemize} \\
\hline
\textbf{Adverse effect/toxicity} & \begin{itemize} \item Usually well tolerated \item Nausea, transient greenish discoloration of stool, pruritus \item Thyroid enlargement, possible neurotoxic effects (related to iodine after considerable systemic absorption, e.g., due to high doses) \end{itemize} \\
\hline
\textbf{Contraindications} & \begin{itemize} \item Pregnancy \item Hepatic insufficiency \item Hypersensitivity to iodine \end{itemize} \\
\hline
\end{tabular}

\textbf{Paromomycin}
\begin{itemize} \item Aminoglycoside \item May be superior to diloxanide in asymptomatic infection. \item It is only active as luminal amebicide. \end{itemize}

\begin{tabular}{|c|l|}
\hline
\textbf{Mechanism of action} & Protein synthesis inhibitor by interacting with the 16S ribosomal subunit. \\
\hline
\textbf{Clinical uses} & \begin{itemize} \item Asymptomatic intestinal infection (alone) \item Amebic colitis (in conjunction with a nitro-imidazole; can be used alone in very mild cases) \item Cryptosporidiosis in AIDS patients \item Visceral leishmaniasis \end{itemize} \\
\hline
\textbf{Adverse effect/toxicity} & Headaches, dizziness, rashes, arthralgia (due to considerable systemic absorption, e.g., in a patient with renal insufficiency) \\
\hline
\textbf{Contraindications} & \begin{itemize} \item Known hypersensitivity \item Intestinal obstruction \end{itemize} \\
\hline
\end{tabular}

\textbf{Other antibiotics}

Some \textbf{antibiotics} can be used in the treatment of intestinal amebiasis. Examples include \textbf{erythromycin} and \textbf{tetracycline}.
Summary of Antiamebicidal Drug Treatment

<table>
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<tr>
<th>Form of amebiasis</th>
<th>Treatment</th>
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</table>
| Asymptomatic intestinal infection | • Luminal agent (i.e., Diloxanide furoate*, 500 mg 3 times daily × 10 days or  
  • Iodoquinol, 650 mg 3 times daily × 21 days or  
  • Paromomycin, 10 mg/kg 3 times daily × 7 days) |
| Amebic colitis (mild to moderate) | • Metronidazole, 750 mg 3 times daily (or 500 mg i.v. every 6 hours) × 10 days or  
  • Tinidazole, 2 g daily × 3 days plus  
  • Luminal agent |
| Amebic colitis (severe)            | • Metronidazole (same as above) or  
  • Tinidazole, 2 g daily × 3 days plus  
  • Luminal agent |
| Extraintestinal amebiasis         | • Metronidazole (same as above) or  
  • Tinidazole, 2 g daily × 5 days plus  
  • Luminal agent |

*Diloxanide furoate is not available in the United States.

Review Questions

The correct answers can be found below the references.

1. Which of the following statements regarding amebicides is correct?
   A. Diloxanide furoate is the drug of choice in hepatic amebiasis.
   B. Iodoquinol inhibits the protein synthesis of E. histolytica.
   C. Paromomycin is a diaminopyrimidine derivative.
   D. Tinidazole is ineffective in cases of metronidazole resistance.
   E. Metronidazole is used for amebiasis as well as postoperative prophylactic antibiotic therapy.

2. Which of the following is the mechanism of action of metronidazole?
   A. Prevents the conversion of heme to hemozoin
   B. Inhibits the nucleic acid synthesis
   C. Inhibits the pyruvate synthesis
   D. Damages the plasma membrane of amoeba
   E. Inhibits the ATP synthesis in amoeba

3. Which of the following is the first-line drug for invasive amebiasis?
   A. Metronidazole
   B. Paromomycin
   C. Diloxanide Furoate
   D. Nitazoxanide
   E. Iodoquinol

References


Correct answers: 1E, 2B, 3A

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