Chemotherapy of Parasitic Infections

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Learning Objectives

1. To have a working knowledge of important antiparasitic agents.
2. To know the indications of the antiparasitic agents and the limitations.

Introduction

The drug development and discovery for parasitic diseases has gained more attention in the recent past after the appreciation of the novel works by William C. Campbell, Satoshi Ōmura and Youyou Tu on parasite-fighting therapies for discovering effective and novel antiparasitic therapies. C. Campbell and Satoshi Ōmura discovered avermectin, the derivatives of which were proven to be effective against river blindness and lymphatic filariasis. Similarly, artemisinin, a novel antimalarial agent, discovered by Youyou Tu, significantly reduced the mortality and morbidity due to malaria. These two discoveries have revolutionized the treatment of these debilitating diseases and paved newer pathways to the antiparasitic drug discovery process. These have caused a huge impact globally, particularly in the developing countries, where the only way of combating these diseases is by effective chemotherapy. Recently, in 2019, triclabendazole has been recommended for the treatment of fascioliasis, which shows that there is an increased focus on the treatment of parasitic diseases. This chapter broadly reviews the antiparasitic agents used to treat both protozoal and other infections.

Goals of Chemotherapy

A multidimensional approach is needed for effective control of parasitic diseases. Mass drug administration through long-term community health programmes and increased awareness of parasitic disease are important in containment of parasitic diseases globally. Successful management of parasitic disease by antiparasitic drug therapy in rare diseases is also equally important. A coordinated approach between nursing care for appropriate monitoring and clinical pharmacists to monitor and avoid dosing, administration error and potential drug–drug interactions in chemotherapy of parasitic infection are crucial. The severe adverse drug reactions observed with many cases during antiparasitic therapy have led

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to many compliance issues. Hence the role of direct observed therapy by healthcare workers benefits the outcomes of community health outreach programmes. Finally, there is a continuous need for research and development for newer drug molecules, potentially safe to combat resistance and treat parasitic infections, especially neglected tropical parasitic diseases.

Antiparasitic Agents

The key principles of use of antiparasitic agents include selecting an appropriate drug for appropriate indication, right dosage according to the individual conditions (age, comorbid conditions, drug-to-drug interactions) and right duration of treatment.

The antiparasitic drugs are broadly classified into antiprotozoals and anthelmintics (Fig. 1). The drugs effective against protozoal infections such as amoebiasis, leishmaniasis, toxoplasmosis, trypanosomal infections, trichomoniasis, malaria, etc. are antiprotozoals, whereas the drugs effective against cestodes, trematodes, nematodes and ectoparasites are categorized under anthelmintics.

Limited efficacy and potency of antiparasitic agents, high toxicity of the drug prevention, and their use in mass administration and development of resistance are the frequently encountered challenges with antiparasitic agents.

Chemotherapy of Protozoal Infections

Chemotherapy of Gastrointestinal Protozoa

Antiamoebic agents include metronidazole, tinidazole, secnidazole, ornidazole, satranidazole, paromomycin and iodoquinol.

Metronidazole, secnidazole, ornidazole, satranidazole and tinidazole are 5-nitroimidazole derivatives. Metronidazole (dose, 500–750 mg PO tid for 7–10 days) has activity against various protozoal infections including giardiasis and trichomoniasis. It acts by producing reactive toxic intermediates within the parasite, thus making it effective as both luminal and extraluminal amoebicide. Metronidazole metabolizes into acid metabolites and hydroxymetabolites. The latter act on the parasitic deoxyribonucleic acid (DNA) and cause DNA disruption, leading to inhibition of protein synthesis. Other nitroimidazoles have similar actions to that of metronidazole with high cure rate, long half-life and better toxicity profile for protozoal infections.

Paromomycin is an aminoglycoside antibiotic that acts by inhibiting parasite 30S ribosome resulting in inhibition of protein synthesis. Iodoquinol is a halogenated hydroxyquinoline which acts as a chelating agent. The compound

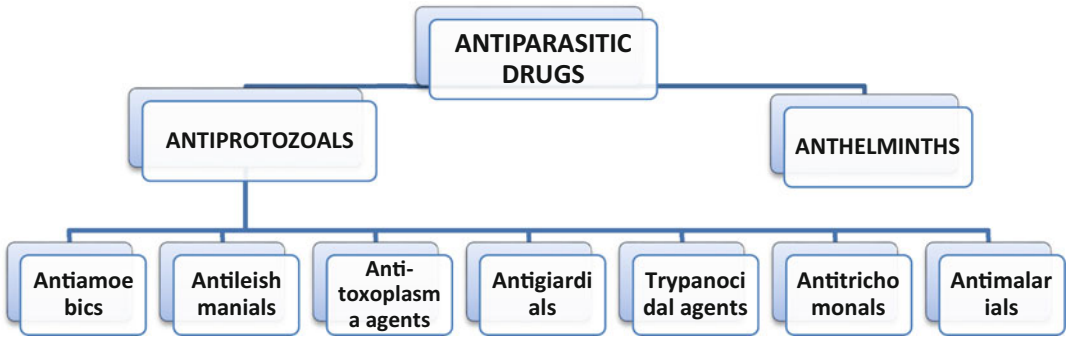

Fig. 1 Classification of antiparasitic agents

within the parasite reduces ferrous ions, thereby increasing protein-bound serum iodine and finally interfering with protozoal metabolism.

The clinical setting determines the choice of drugs used in amoebiasis. Asymptomatic intestinal infection caused by *Entamoeba histolytica* in adults is managed by treatment with luminal agents such as diloxanide furoate, iodoquinol or paromomycin. In mild to moderate and severe intestinal infection, metronidazole or tinidazole along with luminal agent is prescribed. The alternative treatment includes the use of luminal agent along with tetracycline or erythromycin. Metronidazole or tinidazole along with a luminal agent is used for the treatment of extra-intestinal amoebic infections. Iodoquinol is used for treatment of *Dientamoeba fragilis* infection.

Metronidazole and tinidazole are effective against giardiasis caused by *Giardia lamblia*. Paromomycin is recommended for treatment of giardiasis in pregnancy. Nitazoxanide and furazolidone are used in treatment of giardiasis resistant to metronidazole and tinidazole. *Balantidium coli* infection is treated best with tetracycline and alternatively with metronidazole.

Nitazoxanide is effective for treatment of cryptosporidiosis. Co-trimoxazole (trimethoprim 160 mg – plus sulfamethoxazole 800 mg) twice daily for 10 days is effective for treatment of *Isospora belli* and *Cyclospora cayetanensis* infections. Albendazole is the first drug of choice for the treatment of microsporidiosis. Paromomycin is the alternative drug.

Chemotherapy of Genital Protozoa

Anti-trichomonal agents include metronidazole and tinidazole. Metronidazole and tinidazole are the drugs of choice for treatment of infections caused by *Trichomonas vaginalis*. Metronidazole given orally in a single dose of 2 g or 250 mg three times daily for 7 days is effective. Tinidazole given in a single oral dose of 2 g is very effective for treatment of trichomonas infections resistant to metronidazole.

Chemotherapy of Blood and Tissue Protozoa

Sodium stibogluconate and meglumine antimoniate are pentavalent antimonial compounds. They act by decreasing viability of *Leishmania* spp. by inhibiting their glycolysis and citric acid cycle by preventing the conversion of ADP and GDP to ATP and GTP. An antifungal agent such as amphotericin B liposomal preparation acts by binding to an ergosterol precursor of the parasite and disrupting the parasite's membrane. Miltefosine, a derivative of alkylphosphocholine, acts by preventing synthesis of parasite cell surface molecules or by interfering in lipid metabolism of the parasite resulting in disruption of parasite cell signal transduction.

Sodium stibogluconate is prescribed at a dose of 20 mg Sb/kg/day IV or IM for a duration of 28 days to treat visceral leishmaniasis and 20 days for treatment of cutaneous leishmaniasis. Miltefosine given for 28 days, paromomycin for 21 days at a dose of 15 mg/kg/day IM or amphotericin, preferably liposomal preparations, is also effective. Pentamidine at a dose of 2–3 mg/kg IV or IM daily for 15–30 days in visceral leishmaniasis and meglumine antimoniate are the alternate drugs used effectively for intralesional application in leishmaniasis.

Both nifurtimox (8–10 mg/kg/day PO in three to four divided doses for 90 days) and benznidazole (5–7 mg/kg/day PO in two divided doses for 60 days) are the drugs of choice against Chagas disease caused by *Trypanosoma cruzi.* Both these compounds, on activation by parasite mitochondrial nitroreductase, result in the formation of intracellular nitro radical anions. These anions subsequently form a covalent attachment with parasite macromolecules resulting in cellular damage and death of the parasite.

Pentamidine isethionate 4 mg/kg/day IM or IV for 7 days and suramin sodium 100 mg IV followed by 1 g IV on days 1, 3, 5, 14 and 21 are effective against hemolymphatic stage, while melarsoprol 2.2 mg/kg/day IV for 10 days and eflornithine 400 mg/kg/day IV in four doses

for 14 days are effective against CNS stage of *Trypanosoma brucei* causing sleeping sickness.

Melarsoprol is a pro-drug metabolized to an active metabolite melarsen oxide. The mechanism of action of this drug is still unknown. It is suggested that melarsen oxide-trypanothione acts as an inhibitor of trypanothione reductase resulting in the formation of adducts and reduce trypanothione levels of the parasite. The reduction of trypanothione reductase may have a lethal effect on parasitic cells.

Anti-toxoplasma agents include pyrimethamine, sulfadiazine, clindamycin and spiramycin. Pyrimethamine and clindamycin along with folinic acid are recommended for treatment of acute, congenital and immunocompromised toxoplasmosis. Alternatively, pyrimethamine and sulfadiazine along with folinic acid are used. In case of pregnancy, spiramycin, 1 g three times per day until delivery, is recommended. Pyrimethamine prevents DNA and protein synthesis in the parasite by inhibiting dihydrofolate synthase. Sulfadiazine inhibits dihydropteroate synthase which is essential for folic acid synthesis in the parasite; sulfadiazine together with pyrimethamine is used for its synergistic action against toxoplasmosis.

Antimalarial Agents

Among the five *Plasmodium* species known to cause human infections, *Plasmodium falciparum* causes severe disease and death in humans, whereas *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae* cause less severe disease. *Plasmodium knowlesi* is primarily a parasitic infection of monkeys and has recently been recognized to cause illness and severe disease among humans in Asia.

The species, geographic distribution and severity of the patient's infection determine the choice of drug to treat malaria. Chloroquine is the drug of choice to treat uncomplicated malaria caused by *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. Amodiaquine in combination with artesunate, atovaquone with proguanil and artemether with lumefantrine are used for the treatment of drug-resistant *P. falciparum* infections. Oral quinine is indicated in pregnancy. Primaquine, mefloquine, atovaquone-proguanil and doxycycline are used for chemoprophylaxis in malaria.

Mechanism of Action of Antimalarial Agents

Chloroquine is a 4-aminoquinoline that prevents haeme detoxification and biosynthesis of nucleic acid in the parasite. Amodiaquine and 4-aminoquinolone act by inhibiting haeme polymerase activity, thereby preventing detoxification of haeme. The free haeme accumulated is toxic to the parasite and makes it a better alternative in chloroquine-resistant strains. Quinine and mefloquine also inhibit haeme detoxification inside the food vacuole of the parasite. Lumefantrine, an aryl amino-alcohol group, is highly lipophilic and has a similar mechanism of action as quinolones, but it is prescribed only as a fixed combination since it is not recommended for monotherapy.

Primaquine acts by producing free radical-induced damage to the parasite by inducing production of intracellular toxic oxidative changes. Tafenoquine has a long plasma t½ of 16–19 days compared to 6–8 h of primaquine and thus reduces treatment to 3 days compared to 14 days with primaquine. Doxycycline is a broad-spectrum antibiotic that acts against the malarial parasite by disturbing the normal functions of malarial apicoplasts. Atovaquone inhibits the parasite cytochrome electron transport system, and proguanil inhibits dihydrofolate reductase, and thus both act synergistically by inhibiting folic acid synthesis in the malarial parasite.

Artemisinin (*qinghaosu*) is the active component of Chinese herbal medicine known for its antipyretic effect for over 2000 years. The drug is a sesquiterpene lactone endoperoxide, the exact mechanism of action of which is not known. Nevertheless, it is suggested that the iron-catalysed cleavage of the artemisinin endoperoxide bridge in the parasite food vacuole leads to formation of free radicals. These free radicals induce damage and lysis of the parasite or act by inhibiting plasmodial sarcoplasmic-endoplasmic

Table 1 Antimalarial drugs

Drug	Dosage schedule	Adverse side effects
Chloroquine	1 g (600 mg base) PO, then 500 mg (300 mg base) 6 h later, then 500 mg (300 mg base) at 24 and 48 h	Retinopathy, methemoglobinemia, pruritus, muscle weakness
Quinine	650 mg PO q8h × 3 or 7 days	Cinchonism
Mefloquine	750 mg PO followed 12 h later by 500 mg	Seizure, QT prolongation, neuropsychiatric symptoms
Primaquine	30 mg base/d PO × 14 days	Haemolytic anaemia
Sulfadoxine-pyrimethamine	500 mg/25 mg tab as single dose	Megaloblastic anaemia, Stevens-Johnson syndrome, toxic epidermal necrolysis
Atovaquone-proguanil	1g/400 g (adult Tablets Strength) PO once/day for 3 days	Gastrointestinal symptoms, headache
Doxycycline	100 mg PO bid × days	Gastrointestinal symptoms, photosensitivity, tooth discolouration in children
Artemether-lumefantrine	20 mg/120 mg of six doses over 3 days (4 tabs/dose at 0, 8, 24, 36, 48 and 60 h)	Haemolytic anaemia, bradycardia
Artesunate	2.4 mg/kg/dose IV for 3 days at 0, 12, 24, 48 and 72 h	Haemolytic anaemia, bradycardia

calcium ATPase labelled 'Pf ATP6' in the parasite. The newer drug pyronaridine, a Mannich base acridine, has also been studied as an antimalarial for many years. It has a similar mechanism of action to chloroquine and is now available in combination with artesunate.

Quinine is very effective in complicated falciparum malaria. Quinine in combination with clindamycin and atovaquone with azithromycin are used effectively for treatment of *Babesia microti* infection. The antimalarial drugs dosage and common adverse effects are summarized in Table 1.

Chemotherapy of Helminthic Infections

The therapeutic goals of anti-helminthic drugs include elimination of parasites, prevention of transmission and control of infections. The anthelminthic agents act against parasites by interfering with their neuromuscular functions, microtubular structure, calcium permeability or energy metabolism, thereby causing death of the parasite. Poor efficacy of therapy against certain parasites and frequent re-infection in endemic areas which require mass treatment campaigns are a few of the challenges faced during chemotherapy of helminthic infections.

Chemotherapy of Cestodes and Trematodes

Praziquantel acts by increasing the influx of calcium from endogenous stores of both cestodes and trematodes, leading to an intense muscular contraction of the parasite followed by its expulsion. Niclosamide acts by blocking ATP synthesis leading to death and expulsion of the parasite from the body.

Metrifonate is an organophosphorus compound that acts by inactivating acetylcholinesterases of the parasite. This leads to depolarizing neuromuscular blockade followed by expulsion of the parasite. Oxamniquine acts by intercalation of the parasite DNA, leading to blockade of nucleic acid and protein synthesis causing death of the parasite. Triclabendazole is a benzimidazole that acts by inhibiting parasite microtubule formation and protein synthesis. Bithionol blocks ATP synthesis and inhibits parasite energy derived from anaerobic energy metabolism leading to death.

Chemotherapy of Nematodes

The broad-spectrum benzimidazole group of drugs such as thiabendazole, mebendazole, albendazole and triclabendazole have lethal effects on the cytoskeletal structure of the

parasite. The cytoskeletal structure of nematodes includes microfilaments, microtubules and beta-tubulins. They act by inhibiting microtubule synthesis. Benzimidazole binds to beta-tubulins and prevents their assembly leading to inhibition of microtubule formation, followed by inhibition of glucose uptake leading to depletion of parasite glucose stores resulting in reduced ATP formation and death.

Piperazine activates the GABA-gated chloride channel in the nematode leading to flaccid paralysis and also produces a depressed acetylcholine response followed by expulsion of live parasites. Pyrantel pamoate inhibits the parasite's acetylcholine esterase and acts as an agonist at the cholinergic receptor, which leads to depolarizing neuromuscular blockade, thereby causing parasite paralysis. This leads to attachment failure within host intestinal lumen followed by expulsion from the host. Diethylcarbamazine acts by altering the membrane surface characteristics of microfilariae, thereby exposing them to phagocytosis, thus reducing the number of circulating parasites in the blood circulation. Ivermectin is a nematode-specific glutamate-gated agonist activating chloride channels in the parasite pharyngeal muscles leading to hyperpolarization and paralysis.

Chemotherapy of Ectoparasites

Permethrin, ivermectin, hexachlorocyclohexane, crotamiton, sulphur, malathion and benzyl alcohol are used for treatment of infections caused by ectoparasites such as lice and scabies.

Permethrin is toxic to *Pediculus humanus*, *Pthirus pubis* and *Sarcoptes scabiei*. Pyrethroids act on the neuromuscular system causing neurological paralysis by altering sodium and potassium channels on nerve membrane. Ivermectin is approved for head lice treatment as lotion and applied to the hair and scalp, but has limited use. Lindane is a gamma isomer of hexachlorocyclohexane, effective as a shampoo against *Pediculosis capitis* or *Pediculosis pubis*. It acts by affecting the nervous system by penetrating the chitinous layer, thereby killing lice and mites. Combining lindane with benzyl benzoate prevents development of resistance and improves cure rate.

Crotamiton (10%) cream or lotion is a scabicide and pediculicide with antipruritic properties. Because of lower efficacy and repeated application, it is the second choice as a scabicide and pediculicide. Malathion and dicophane are insecticides, poorly absorbed through the skin but able to penetrate the exoskeleton and act as an arthropod neurotoxin, but are rarely used. Sulphur, which is non-irritating to the skin, is the oldest scabicide used. On coming in contact with the skin, sulphur is reduced to hydrogen sulphide and gets oxidized to sulphur dioxide and pentathionic acid, which is lethal to arthropods. However, the compound has an unpleasant odour with staining; thus patient compliance is poor.

Drug Resistance

The emergence of drug resistance in parasites to the available drugs is a major challenge. Chloroquine-resistant *P. falciparum*, metronidazole-resistant *Giardia*, sulfonamide-resistant *Toxoplasma gondii* and diloxanide-resistant *E. histolytica* are a few examples of emerging drug resistance in parasites of public health importance.

Several molecular mechanisms are suggested to play an important role in the development of drug resistance among parasites (Table 2). The efflux process through efflux transporters such as P glycoprotein is one major mechanism suggested for development of resistance in parasites. Evidence supports that this kind of resistance can be partially reversed with verapamil. Other mechanisms include alteration in the affinity of binding or the structure of the target receptor (levamisole target acetylcholine nicotinic receptor). Emergence of drug resistance in parasites can be reduced or prevented using a combination of drugs with different mechanisms of action such

Table 2 Mechanism of action and mechanisms of resistance of commonly used antiparasitic agents

Drug	Mechanism of action	Mechanism of resistance
Chloroquine	Haemozoin formation from the haeme is inhibited, and this free haeme leads to parasite death by lyses of its membranes	Due to altered transport properties, there will be a decreased accumulation of the drugs inside the parasite
Artemisinins	Mechanism is unknown. Ideas are controversial, and they are proposed as (1) artemisinin-derived free radicals induce damage and lysis of the parasite or (2) act by inhibiting plasmodial sarcoplasmic-endoplasmic calcium ATPase labelled as 'Pf ATP6'	Mechanism is unknown
Metronidazole	Acts against the parasite by producing reactive toxic intermediates within the parasite. It metabolizes into acid metabolites and hydroxymetabolites of which it later acts on the parasitic deoxyribonucleic acid (DNA) and causes DNA disruption, leading to inhibition of protein synthesis	Decreases level of enzymes necessary for the activation of nitro group
Miltefosine	Prevents synthesis of parasite cell surface molecules or by interfering lipid metabolism of the parasite resulting in disruption of parasite cell signal transduction	Increased drug efflux
Albendazole	Binds to beta-tubulins and prevents their polymerization, followed by inhibition of glucose uptake leading to depletion of parasite glucose stores resulting in reduced ATP formation and death	Alteration in the high-affinity binding to β-tubulin of the parasites
Praziquantel	Increases the influx of calcium from endogenous stores of both cestodes and nematodes, leading to intense muscular paralysis of the parasites	Increased drug efflux

Table 3 Chemotherapy of parasites

• High-dose albendazole used longer than 3 months (as for hydatid disease) may cause hepatotoxicity
• Ivermectin should be avoided in children below 5 years old and has recently been approved for topical treatment of inflammatory lesions of rosacea
• Fastest-acting drugs against malaria are artemisinins
• Miltefosine can be administered orally for kala-azar
• Albendazole is the drug of choice for all nematode infestations including cutaneous larva migrans, visceral larva migrans and neurocysticercosis **except** *Enterobius* (mebendazole), *Wuchereria bancrofti* and *Brugia malayi* (DEC), *Onchocerca* and *Strongyloides* (ivermectin) and *Dracunculus* (metronidazole)
• The drug of choice for all trematode and cestode infections is praziquantel except *Fasciola hepatica* (triclabendazole) and hydatid disease (albendazole)

as artemisinin-based combination therapies (ACTs) in malaria and also by preventing the misuse of drugs.

Antiparasitic drugs (Table 3) are highly insoluble, and hence to increase their clinical effectiveness, they are given in large doses. To overcome this, scientists have developed a new way to deliver these drugs more efficiently by using nanotechnology. They have developed a novel nano-capsule formulation of triclabendazole (drug used for fascioliasis) to enhance its efficacy and reduce its toxic effects. Abametapir-A is an example of such a new drug being recently recommended for the treatment of *Pediculosis capitis* infections.

Case Study

A 19-year-old boy was admitted to casualty with severe abdominal pain, fever and bloody diarrhoea. On examination vitals were stable, and the patient was mildly dehydrated. The stool sample was sent for examination and it was positive for *E. histolytica*. The patient was admitted for 1 day and discharged with advice to take metronidazole 750 mg PO tid for 7 days. On the fourth day of treatment, the patient returned with dizziness, throbbing headache, chest and abdominal discomfort but no diarrhoea. History of alcohol consumption was noted.

1. Rationalize the cause for the symptoms presented on the fourth day of treatment.
2. Suggest a suitable plan of management for the above case.
3. What are the alternative drugs which can be used in this condition?

Research Questions

1. How to improve the discovery of antiparasitic drugs which are limited in number and sometimes ineffective because of resistance?
2. How is the incomplete knowledge of the mechanism of action of many antiparasitic agents leading to poor understanding of their toxicity and resistance pattern?
3. How is the lack of availability of effective vaccines playing a challenging role in controlling parasitic infections?

Further Readings

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