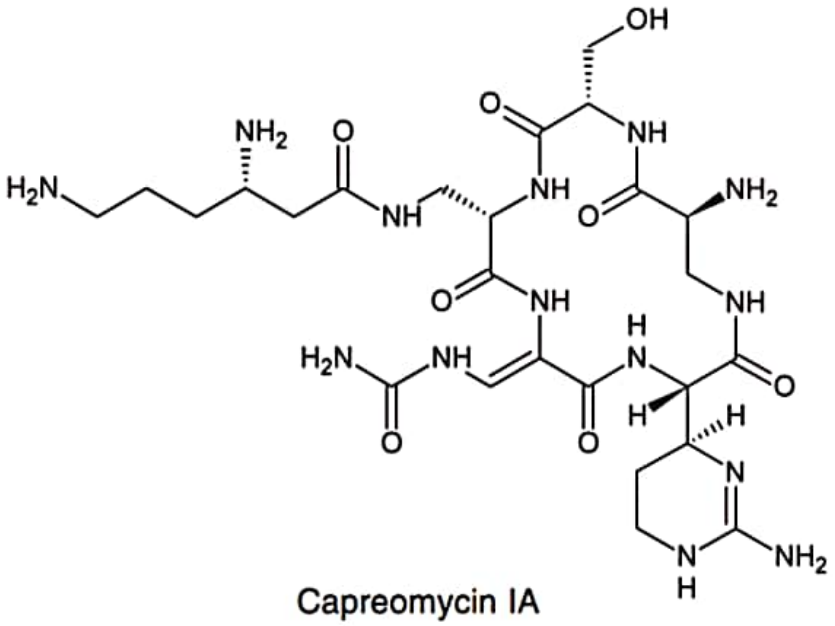


Capreomycin IA

Four capreomycins, designated IA, IB, IIA, and IIB, have been isolated from cultures of *S. capreolus*. The clinical agent contains primarily IA and IB. The close chemical relationship between capreomycins IA and IB and viomycin was established,[87] and the total synthesis and proof of structure of the capreomycins were later accomplished.[88] The structures of capreomycins IIA and IIB correspond to those of IA and IB but lack the β-lysyl residue. The sulfate salts are freely soluble in water.

ANTIPROTOZOAL AGENTS

In the United States and other countries of the temperate zone, protozoal diseases are of minor importance, whereas bacterial and viral diseases are widespread and are the cause of considerable concern. On the other hand, protozoal diseases are highly prevalent in tropical Third World countries, where they infect both human and animal populations, causing suffering, death, and enormous economic hardship. Protozoal diseases that are found in the United States are malaria, amebiasis, giardiasis, trichomoniasis, toxoplasmosis, and, as a direct consequence of the AIDS epidemic, *P. carinii* pneumonia (PCP).

Although amebiasis is generally thought of as a tropical disease, it actually has a worldwide distribution. In some areas with temperate climates in which sanitation is poor, the prevalence of amebiasis has been estimated to be as high as 20% of the population. The causative organism, *Entamoeba histolytica*, can invade the wall of the colon or other parts of the body (e.g., liver, lungs, skin). An ideal chemotherapeutic agent would be effective against both the intestinal and extraintestinal forms of the parasite.

Amebicides that are effective against both intestinal and extraintestinal forms of the disease are limited to the somewhat toxic alkaloids emetine and dehydroemetine, the nitroimidazole derivative metronidazole, and the antimalarial agent chloroquine (Chapter 7). A second group of amebicides that are effective only against intestinal forms of the disease includes the aminoglycoside antibiotic paromomycin, the 8-hydroxyquinoline derivative iodoquinol, the arsenical compound carbarsone, and diloxanide.

Other protozoal species that colonize the intestinal tract and cause enteritis and diarrhea are *Balantidium coli* and the flagellates, *G. lamblia* and *Cryptosporidium* spp. Balantidiasis responds best to tetracycline. Metronidazole and iodoquinol may also be effective. Giardiasis may be treated effectively with furazolidone, metronidazole, or the antimalarial drug quinacrine (Chapter 7). Cryptosporidiosis is normally self-limiting in immunocompetent patients and is not normally treated. The illness can be a serious problem in AIDS patients because no effective therapy is currently available.

Trichomoniasis, a venereal disease caused by the flagellated protozoan *T. vaginalis*, is common in the United States and throughout the world. Although it is not generally considered serious, this affliction can cause serious physical discomfort. Oral metronidazole provides effective treatment against all forms of the disease. It is also used to eradicate the organism from asymptomatic male carriers.

P. carinii is an opportunistic pathogen that may colonize the lungs of humans and other animals and, under the right conditions, can cause pneumonia. The organism has long been classified as a protozoan, but recent RNA evidence suggests that it may be more closely related to fungi. At one time, occasional cases of PCP were known to occur in premature, undernourished infants and in patients receiving immunosuppressant therapy. The situation changed with the onset of the AIDS epidemic. It is estimated that at least 60% and possibly as high as 85% of patients infected with HIV develop PCP during their lifetimes.

The combination of the antifolate trimethoprim and the sulfonamide sulfamethoxazole constitutes the treatment of choice for PCP. Other effective drugs include pentamidine, atovaquone, and a new antifolate, trimetrexate.

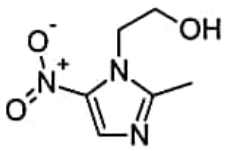
Toxoplasma gondii is an obligate intracellular protozoan that is best known for causing blindness in neonates. Toxoplasmosis, the disseminated form of the disease in which the lymphatic system, skeletal muscles, heart, brain, eye, and placenta may be affected, has become increasingly prevalent in association with HIV infection. A combination of the antifolate pyrimethamine and the sulfa drug sulfadiazine constitutes the most effective therapy for toxoplasmosis.

Various forms of trypanosomiasis, chronic tropical diseases caused by pathogenic members of the family Trypanosomidae, occur both in humans and in livestock. The principal disease in humans, sleeping sickness, can be broadly classified into two main geographic and etiological groups: African sleeping sickness caused by *Trypanosoma gambiense* (West African), *Trypanosoma rhodesiense* (East African), or *Trypanosoma congolense*; and South American sleeping sickness (Chagas disease) caused by *Trypanosoma cruzi*. Of the various forms of trypanosomiasis, Chagas disease is the most serious and generally the most resistant to chemotherapy. Leishmaniasis is a chronic tropical disease caused by various flagellate protozoa of the genus *Leishmania*. The more common visceral form caused by *Leishmania donovani*, called *kala-azar*, is similar to Chagas disease. Although these diseases are widespread in tropical areas of Africa and South and Central America, they are of minor importance in the United States, Europe, and Asia.

Chemotherapy of trypanosomiasis and leishmaniasis remains somewhat primitive and is often less than effective. In fact, it is doubtful that these diseases can be controlled by chemotherapeutic measures alone, without successful control of the intermediate hosts and vectors that transmit them. Heavy metal compounds, such as the arsenicals and antimonials, are sometimes effective but frequently toxic. The old standby suramin appears to be of some value in long- and short-term prophylaxis. The nitrofuran derivative nifurtimox may be a major asset in the control of these diseases, but its potential toxicity remains to be fully determined.

Metronidazole

2-Methyl-5-nitroimidazole-1-ethanol (Flagyl, Protostat, Metro IV) is the most useful of a group of antiprotozoal nitroimidazole derivatives that have been synthesized in various laboratories throughout the world. Metronidazole was first marketed for the topical treatment of *T. vaginalis* vaginitis. It has since been shown to be effective orally against both the acute and carrier states of the disease. The drug also possesses useful amebicidal activity and is, in fact, effective against both intestinal and hepatic amebiasis. It has also been found of use in the treatment of such other protozoal diseases as giardiasis and balantidiasis.



More recently, metronidazole has been found to possess efficacy against obligate anaerobic bacteria, but it is ineffective against facultative anaerobes or obligate aerobes. It is particularly active against Gram-negative anaerobes, such as *Bacteroides* and *Fusobacterium* spp. It is also effective against Gram-positive anaerobic bacilli (e.g., *Clostridium* spp.) and cocci (e.g., *Peptococcus*, *Peptidostreptococcus* spp.). Because of its bactericidal action, metronidazole has become an important agent for the treatment of serious infections (e.g., septicemia, pneumonia, peritonitis, pelvic infections, abscesses, meningitis) caused by anaerobic bacteria.

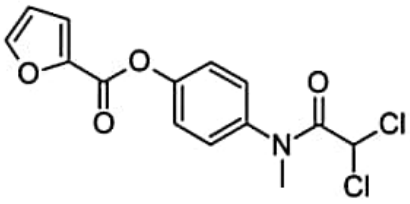
The common characteristic of microorganisms (bacteria and protozoa) sensitive to metronidazole is that they are anaerobic. It has been speculated that a reactive intermediate formed in the microbial reduction of the 5-nitro group of metronidazole covalently binds to the DNA of the microorganism, triggering the lethal effect.[89] Potential reactive intermediates include the nitroxide, nitroso, hydroxylamine, and amine. The ability of metronidazole to act as a radiosensitizing agent is also related to its reduction potential.

Metronidazole is a pale yellow crystalline substance that is sparingly soluble in water. It is stable in air but is light sensitive. Despite its low water solubility, metronidazole is well absorbed following oral administration. It has a large apparent volume of distribution and achieves effective concentrations in all body fluids and tissues. Approximately 20% of an oral dose is metabolized to oxidized or conjugated forms. The 2-hydroxy metabolite is active; other metabolites are inactive.

Metronidazole is a weak base that possesses a pK_a of 2.5. Although it is administered parenterally only as the free base by slow intravenous infusion, metronidazole for injection is supplied in two forms: a ready-to-inject 100-mL solution containing 5 mg of base per mL; and a hydrochloride salt as 500 mg of a sterile lyophilized powder. Metronidazole hydrochloride for injection must first be reconstituted with sterile water to yield 5 mL of a solution having a concentration of 100 mg/mL and a pH ranging from 0.5 to 2.0. The resulting solution must then be diluted with either 100 mL of normal saline or 5% dextrose and neutralized with 5 mEq of sodium bicarbonate to provide a final solution of metronidazole base with an approximate concentration of 5 mg/mL and a pH of 6 to 7. Solutions of metronidazole hydrochloride are unsuitable for intravenous administration because of their extreme acidity. Reconstituted metronidazole hydrochloride solutions are stable for 96 hours at 30°C, whereas ready-to-use solutions of metronidazole base are stable for 24 hours at 30°C. Both solutions should be protected from light.

Diloxanide

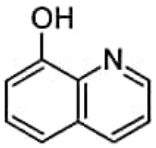
Furamide, or eutamide, is the 2-furoate ester of 2,2-dichloro-4′-hydroxy-*N*-methylacetanilide. It was developed as a result of the discovery that various α,α-dichloroacetamides possessed amebicidal activity in vitro. Diloxanide itself and many of its esters are also active, and drug metabolism studies indicate that hydrolysis of the amide is required for the amebicidal effect. Nonpolar esters of diloxanide are more potent than polar ones. Diloxanide furoate has been used in the treatment of asymptomatic carriers of *E. histolytica*. Its effectiveness against acute intestinal amebiasis or hepatic abscesses, however, has not been established. Diloxanide furoate is a white crystalline powder. It is administered orally only as 500-mg tablets and may be obtained in the United States from the CDC in Atlanta, Georgia.



8-Hydroxyquinoline

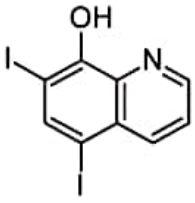
Oxine, quinophenol, or oxyquinoline is the parent compound from which the antiprotozoal oxyquinolines have been derived. The antibacterial and antifungal properties of

oxine and its derivatives, which are believed to result from the ability to chelate metal ions, are well known. Aqueous solutions of acid salts of oxine, particularly the sulfate (Chinosol, Quinosol), in concentrations of 1:3,000 to 1:1,000, have been used as topical antiseptics. The substitution of an iodine atom at the 7-position of 8-hydroxyquinolines yields compounds with broad-spectrum amebicidal properties.



Iodoquinol

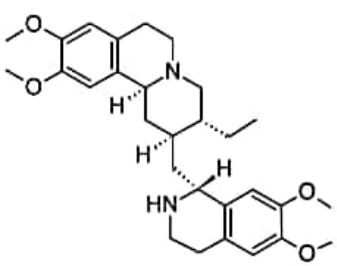
5,7-Diiodo-8-quinolinol, 5,7-diiodo-8-hydroxyquinoline, or diiodohydroxyquin (Yodoxin, Diodoquin, Diquinol) is a yellowish to tan microcrystalline, light-sensitive substance that is insoluble in water. It is recommended for acute and chronic intestinal amebiasis but is not effective in extraintestinal disease. Because a relatively high incidence of topic neuropathy has occurred with its use, iodoquinol should not be used routinely for traveler's diarrhea.

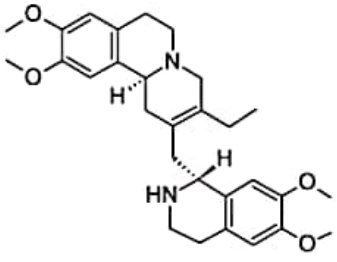


Emetine and Dehydroemetine

The alkaloids emetine and dehydroemetine are obtained by separation from extracts of ipecac. They occur as levorotatory, light-sensitive white powders that are insoluble in water. The alkaloids readily form water-soluble salts. Solutions of the hydrochloride salts intended for intramuscular injection should be adjusted to pH 3.5 and stored in light-resistant containers.

Emetine and dehydroemetine exert a direct amebicidal action on various forms of *E. histolytica*. They are protoplasmic poisons that inhibit protein synthesis in protozoal and mammalian cells by preventing protein elongation. Because their effect in intestinal amebiasis is solely symptomatic and the cure rate is only 10% to 15%, they should be used only in combination with other agents. The high concentrations of the alkaloids achieved in the liver and other tissues after intramuscular injection provide the basis for their high effectiveness against hepatic abscesses and other extraintestinal forms of the disease. Toxic effects limit the usefulness of emetine. It causes a high frequency of gastrointestinal distress (especially nausea and diarrhea), cardiovascular effects (hypotension and arrhythmias), and neuromuscular effects (pain and weakness). A lower incidence of cardiotoxicity has been associated with the use of dehydroemetine (Mebadin), which is available from the CDC and is also amebicidal.

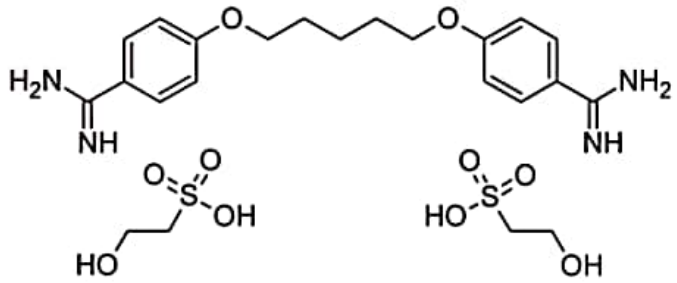




Emetine and dehydroemetine have also been used to treat balantidial dysentery and fluke infestations, such as fascioliasis and paragonimiasis.

Pentamidine Isethionate

4,4′-(Pentamethylenedioxy)dibenzamidine diisethionate (NebuPent, Pentam 300) is a water-soluble crystalline salt that is stable to light and air. The principal use of pentamidine is for the treatment of pneumonia caused by the opportunistic pathogenic protozoan *P. carinii*, a frequent secondary invader associated with AIDS. The drug may be administered by slow intravenous infusion or by deep intramuscular injection for PCP. An aerosol form of pentamidine is used by inhalation for the prevention of PCP in high-risk patients infected with HIV who have a previous history of PCP infection or a low peripheral $CD4^+$ lymphocyte count.

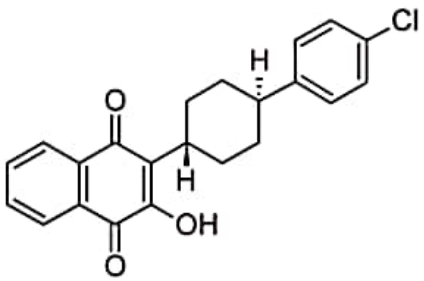


Both the inhalant (aerosol) and parenteral dosage forms of pentamidine isethionate are sterile lyophilized powders that must be made up as sterile aqueous solutions prior to use. Sterile water for injection must be used to reconstitute the aerosol, to avoid precipitation of the pentamidine salt. Adverse reactions to the drug are common. These include cough and bronchospasm (inhalation) and hypertension and hypoglycemia (injection).

Pentamidine has been used for the prophylaxis and treatment of African trypanosomiasis. It also has some value for treating visceral leishmaniasis. Pentamidine rapidly disappears from the plasma after intravenous injection and is distributed to the tissues, where it is stored for a long period. This property probably contributes to the usefulness of the drug as a prophylactic agent.

Atovaquone

3-[4-(4-Chlorophenyl)-cyclohexyl]-2-hydroxy-1,4-naphthoquinone (Mepron) is a highly lipophilic, water-insoluble analog of ubiquinone 6, an essential component of the mitochondrial electron transport chain in microorganisms. The structural similarity between atovaquone and ubiquinone suggests that the former may act as an antimetabolite for the latter and thereby interfere with the function of electron transport enzymes.

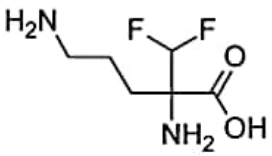


Atovaquone was originally developed as an antimalarial drug, but *Plasmodium falciparum* was found to develop a rapid tolerance to its action. More recently, the effectiveness of atovaquone against *P. carinii* was discovered. It is a currently recommended alternative to trimethoprim-sulfamethoxazole (TMP-SMX) for the treatment and prophylaxis of PCP in patients intolerant to this combination. Atovaquone was also shown to be effective in eradicating *T. gondii* in preclinical animal studies.

The oral absorption of atovaquone is slow and incomplete, in part because of the low water solubility of the drug. Aqueous suspensions provide significantly better absorption than do tablets. Food, especially if it has a high fat content, increases atovaquone absorption. Significant enterohepatic recycling of atovaquone occurs, and most (nearly 95%) of the drug is excreted unchanged in the feces. In vivo, atovaquone is largely confined to the plasma, where it is extensively protein bound (>99.9%). The half-life of the drug ranges from 62 to 80 hours. The primary side effect is gastrointestinal intolerance.

Eflornithine

Eflornithine is used for the treatment of West African sleeping sickness, caused by *Trypanosoma brucei gambiense*. It is specifically indicated for the meningoencephalitic stage of the disease. Eflornithine is a myelosuppressive drug that causes high incidences of anemia, leukopenia, and thrombocytopenia. Complete blood cell counts must be monitored during the course of therapy.

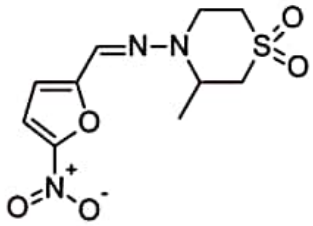


The irreversible inactivation of ornithine decarboxylase by eflornithine is accompanied by decarboxylation and release of fluoride ion from the inhibitor,[90] suggesting enzyme-catalyzed activation of the inhibitor. Only the (−) isomer, stereochemically related to L-ornithine, is active.

Eflornithine is supplied as the hydrochloride salt. It may be administered either intravenously or orally. Approximately 80% of the unchanged drug is excreted in the urine. Penetration of eflornithine into the CSF is facilitated by inflammation of the meninges.

Nifurtimox

Nifurtimox is 4-[(5-nitrofurfurylidene) amino]-3-methylthiomorpholine-1,1-dioxide, or Bayer 2502 (Lampit). The observation that various derivatives of 5-nitrofuraldehyde possessed, in addition to their antibacterial and antifungal properties, significant and potentially useful antiprotozoal activity eventually led to discovery of particular nitrofurans with antitrypanosomal activity.

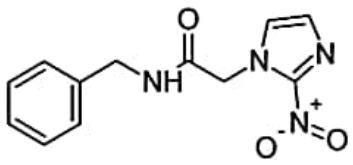


The most important of such compounds is nifurtimox because of its demonstrated effectiveness against *T. cruzi*, the parasite responsible for South American trypanosomiasis. In fact, use of this drug represents the only clinically proven treatment for both acute and chronic forms of the disease. Nifurtimox is available in the United States from the CDC.

Nifurtimox is administered orally. Oral bioavailability is high, but considerable first-pass metabolism occurs. The half-life of nifurtimox is 2 to 4 hours. The drug is poorly tolerated, with a high incidence of nausea, vomiting, abdominal pain, and anorexia reported. Symptoms of central and peripheral nervous system toxicity also frequently occur with nifurtimox.

Benznidazole

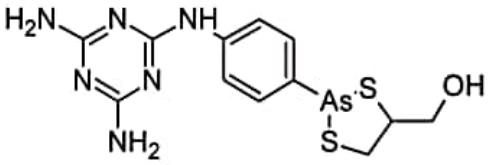
N-Benzyl-2-nitroimidazole-1-acetamide (Radanil, Rochagan) is a nitroimidazole derivative that is used for the treatment of Chagas disease. It is not available in the United States but is used extensively in South America. The effectiveness of benznidazole is similar to that of nifurtimox. Therapy for American trypanosomiasis with oral benznidazole requires several weeks and is frequently accompanied by adverse effects such as peripheral neuropathy, bone marrow depression, and allergic-type reactions.



Melarsoprol

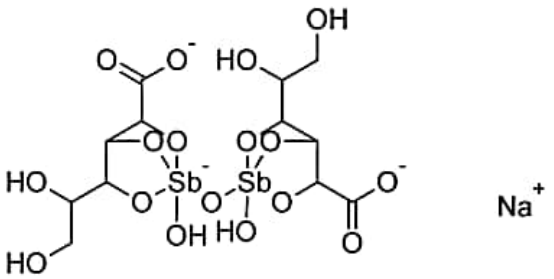
2-*p*-(4,6-Diamino-*s*-triazin-2-yl-amino)phenyl-4-hydroxymethyl-1,3,2-dithiarsoline (Mel B, Arsobal) is prepared by reduction of a corresponding pentavalent arsanilate to the trivalent arsenoxide followed by reaction of the latter with 2,3-dimercapto-1-propanol (British anti-Lewisite [BAL]). It has become the drug of choice for the treatment of the later stages of both forms of African trypanosomiasis. Melarsoprol has the advantage of excellent penetration into the CNS and, therefore, is effective against meningoencephalitic forms of *T. gambiense* and *T. rhodesiense*. Trivalent arsenicals tend to be more toxic to the host (as well as the parasites) than the corresponding pentavalent compounds. The bonding of arsenic with sulfur atoms tends to reduce host toxicity, increase chemical stability (to oxidation), and improve distribution of the compound to the arsenoxide. Melarsoprol shares the toxic properties of other

arsenicals, however, so its use must be monitored for signs of arsenic toxicity.



Sodium Stibogluconate

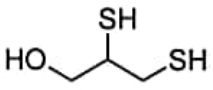
Sodium antimony gluconate (Pentostam) is a pentavalent antimonial compound intended primarily for the treatment of various forms of leishmaniasis. It is available from the CDC as the disodium salt, which is chemically stable and freely soluble in water. The 10% aqueous solution used for either intramuscular or intravenous injection has a pH of approximately 5.5. Like all antimonial drugs, this drug has a low therapeutic index, and patients undergoing therapy with it should be monitored carefully for signs of heavy metal poisoning. Other organic antimonial compounds are used primarily for the treatment of schistosomiasis and other flukes.



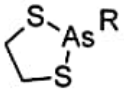
The antileishmanial action of sodium stibogluconate requires its reduction to the trivalent form, which is believed to inhibit phosphofructokinase in the parasite.

Dimercaprol

2,3-Dimercapto-1-propanol, BAL, or dithioglycerol is a foul-smelling, colorless liquid. It is soluble in water (1:20) and alcohol. It was developed by the British during World War II as an antidote for "Lewisite," hence the name British anti-Lewisite or BAL. Dimercaprol is effective topically and systematically as an antidote for poisoning caused by arsenic, antimony, mercury, gold, and lead. It can, therefore, also be used to treat arsenic and antimony toxicity associated with overdose or accidental ingestion of organoarsenicals or organoantimonials.



The antidotal properties of BAL are associated with the property of heavy metals to react with sulfhydryl (SH) groups in proteins (e.g., the enzyme pyruvate oxidase) and interfere with their normal function. 1,2-Dithiol compounds such as BAL compete effectively with such proteins for the metal by reversibly forming metal ring compounds of the following type:

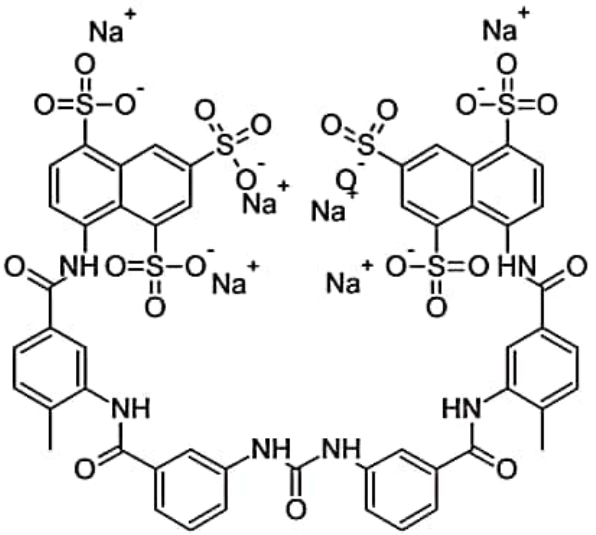


These are relatively nontoxic, metabolically conjugated (as glucuronides), and rapidly excreted.

BAL may be applied topically as an ointment or injected intramuscularly as a 5% or 10% solution in peanut oil.

Suramin Sodium

Suramin sodium is a high–molecular-weight bisurea derivative containing six sulfonic acid groups as their sodium salts. It was developed in Germany shortly after World War I as a byproduct of research efforts directed toward the development of potential antiparasitic agents from dyestuffs.



The drug has been used for more than half a century for the treatment of early cases of trypanosomiasis. Not until several decades later, however, was suramin discovered to be a long-term prophylactic agent whose effectiveness after a single intravenous injection is maintained for up to 3 months. The drug is tightly bound to plasma proteins, causing its excretion in the urine to be almost negligible.

Tissue penetration of the drug does not occur, apparently because of its high molecular weight and highly ionic character. Thus, an injected dose remains in the plasma for a very long period. Newer, more effective drugs are now available for short-term treatment and prophylaxis of African sleeping sickness. Suramin is also used for prophylaxis of onchocerciasis. It is available from the CDC.

ANTHELMINTICS

Anthelmintics are drugs that have the capability of ridding the body of parasitic worms or helminths. The prevalence of human helminthic infestations is widespread throughout the globe and represents a major world health problem, particularly in Third World countries. Helminths parasitic to humans and other animals are derived from two phyla, Platyhelminthes and Nemathelminthes. Cestodes (tapeworms) and trematodes (flukes) belong to the former, and nematodes or true roundworms belong to the latter. The helminth infestations of major concern on the North American continent are caused by roundworms (i.e., hookworm, pinworm, and *Ascaris* spp.). Human