Human Antiparasitic Drugs: Pharmacology and Usage

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Preface

The need for a text devoted exclusively to the pharmacology of antiparasitic drugs became evident to the principal author in the course of teaching pharmacology to medical and science students in the tropics. This need is now more cogent with academic institutions worldwide becoming increasingly involved in the tropical and parasitic diseases. Drugs are an integral factor in parasitic disease studies whether they are employed for their curative and related pharmacological effects or as tools to reveal the nature of the disease processes. A knowledge of their fundamental properties in the context of parasitic disease is therefore mandatory for such studies.

This text is intended primarily as an introduction for those embarking on studies in the tropical and parasitic diseases at the undergraduate and postgraduate levels. It aims to integrate the biological principles of the more common human diseases with the important pharmacological properties of specific drugs that are of value therapeutically. There is also much information of value to the practising clinician especially that relating to drug kinetics, toxicity and dosage regimens.

The first section, which deals with fundamental principles, provides a basis for the two subsequent sections in which the drugs relating to the two subkingdoms (Protozoa and Helminths) are considered. In these latter sections, all drugs in current use as well as those in an advanced stage of development are discussed in detail. Also included, where relevant, are some obsolete drugs which are still of academic interest.

In order to achieve greater coherence and ease of reading, the documentation of references relating to individual findings is excluded. However, the selected texts and reviews which are listed for further reading should yield more extensive information on specific areas, where required.

We are greatly indebted to our colleagues, Dr S.L. Croft, Dr P. Dukes, Dr R.L. Muller and Dr D.C. Warhurst, for reading specialized areas of the text and for their invaluable comments and suggestions. Dr Warhurst kindly provided the photograph of the Corey–Pauling–Koltun model of the quinine structure for inclusion in Fig. 3.3.

Contents

SECTION A

A Background to Parasitic Diseases and Drug Treatment

Chapter 1

General Considerations

Drugs with curative effects against specific diseases are best studied within the context of the biology of the disease conditions they are designed to control. The parasitic diseases of man arise when healthy human tissue is invaded by organisms of an exogenous species belonging to one of the following biological groups: protozoa, helminths, bacteria, fungi, viruses and a few microorganisms of indeterminate classification. The protozoa and helminths together are generally referred to as parasites, or as animal parasites to distinguish them from the other pathogens. This difference is emphasized by the eukaryotic cellular organization typical of all animal parasites and by their complex life-cycles.

1.1 PARASITISM

Parasitism is generally defined as a relationship between two biological species in which one lives in a dependent association with the other. There are many such associations but the type relevant in this context involves two animal species, the parasite and its host, with the parasite invading the body of the larger animal (the host) at some phase of its life cycle. The parasite benefits from the association nutritionally which aids its survival and usually its reproduction. The association may not be detrimental to the host in the absence of environmental stress or ill-health, but host vulnerability is greatly enhanced in the harsh environment of Third World countries.

1.2 HOSTS

Parasites are selective with respect to the host species with which they become associated. The parasite undergoes its life cycle (Fig. 1.1) within a selected host and it may be *direct*, that is to reach completion within the host and to release an infective form which is capable of invading a second host, as in amoebiasis; or *indirect* and require one or two additional hosts to achieve completion. The host in which the parasite attains maturity is referred to as the *definitive* host to distinguish it from the *intermediate* host in which the parasite undergoes another phase of its life-cycle and which is mandatory for its completion, for example, in schistosomiasis. More than one intermediate host may be involved, as in other human trematode diseases.

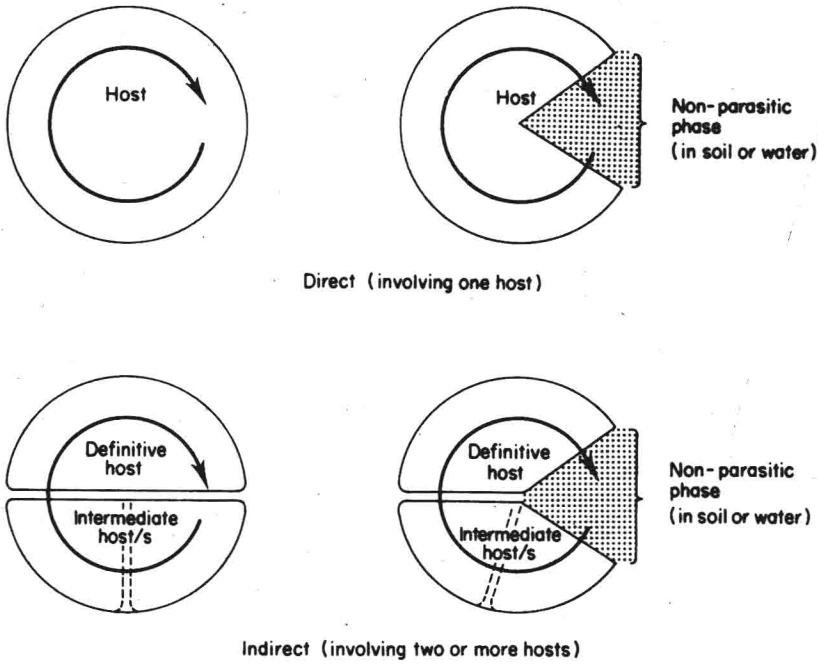

Fig. 1.1 Parasitic life cycle patterns

In either case, there may be a non-parasitic phase in soil or water.

The term *vector* is frequently used synonymously with intermediate host, as for example, the tsetse fly in trypanosomiasis or the snail in schistosomiasis where both terms are applicable, each parasite undergoing part of its life-cycle in the fly or snail before the latter performs the function of transmitting the infective agent to the new host. One must distinguish between such disease-carriers with a dual role from those that are exclusively mechanical carriers of disease for which vector alone is applicable.

The range of hosts which are susceptible to a particular parasite is varied and has an evolutionary basis. Our interest in relation to the spread of parasitic agents, however, lies in the current pattern of this specificity (Table 1.1). Man, his domestic animals and even certain pests often harbour the same parasitic species, but there is considerable variation in the intensity of the invasion and in its outcome in the different host species. For example, some game animals in East Africa harbour, without ill-effect, the trypanosome (*T. rhodesiense*) which is rapidly lethal on transmission to man. The term *reservoir* is applied to host species that can maintain the parasite with low or insignificant morbidity. Reservoir species are usually more stable sources of parasites than are the compromised hosts and often present a greater barrier to disease control. Many domestic animals, and particularly pets, fall into this category, their close proximity to man increasing their significance as reservoir hosts. The importance of

Table 1.1 Main protozoal diseases affecting man

Disease	*Causative organisms*	*Mode of transmission*	*Other natural hosts*	*Z Zoonosis confirmed*	*Geographical distribution*
Trypanosomiasis					
Sleeping sickness and Chagas' disease	*Trypanosoma* spp.	vector: tsetse, reduviid bug	game, domestic and small mammals	Z	Africa, South America
Leishmaniasis					
Kala-azar, tropical sore, espundia	*Leishmania* spp.	vector: sandfly	dogs and small mammals	Z	Africa, South America, Europe and Asia
Trichomoniasis	*Trichomonas vaginalis*	venereal	—	—	world-wide
Giardiasis	*Giardia lamblia*	ingestion	wild mammals	(Z)	world-wide
Amoebiasis	*Entamoeba histolytica*	ingestion	dogs, primates	(Z)	world-wide
Amoebic meningo-encephalitis	*Naegleria fowleri*	nasal m. membrane	domestic animals, rodents	—	world-wide
Toxoplasmosis	*Toxoplasma gondii*	ingestion congenital	domestic and wild animals	Z	world-wide
Malaria	*Plasmodium* spp.	vector: mosquito	—	—	tropical areas
Babesiosis	*Babesia* spp.	vector: tick	cattle, sheep	Z	Europe, America
Pneumocystis pneumonia	*Pneumocystis carinii*	unknown	rodents, dogs	Z	Europe, America
Balantidiasis	*Balantidium coli*	ingestion	pigs	(Z)	Indonesia, Iran

feral species as reservoirs is becoming increasingly apparent with changes in ecosystems, the development of unexploited land bringing humans into closer proximity with wild animal species. The animal parasitic diseases which infect man are termed *parasitic zoonoses* and the term is defined as 'parasitic infections which are naturally transmitted between vertebrate animals and man'. Many of the most serious and widespread human parasitic infections which are confirmed zoonoses are listed in Tables 1.1 and 1.2.

Parasites with a multiplicity of definitive hosts are clearly the more difficult to control. Hosts in which more stable relationships between host and parasite have evolved are relatively unaffected by the association thus ensuring the continued maintenance of the parasite in nature. Most of the recently acquired human parasitic diseases are virulent and often lethal because the parasites have not adapted to the human host.

Table 1.2 Main helminth diseases affecting man

	Disease	*Other natural hosts*	*Z Zoonosis confirmed*	*Geographical distribution*
NEMATODES	*Ascariasis* (roundworm)	pigs	—	world-wide
	Enterobiasis (pin/thread-worm)	—	—	world-wide
	Hookworm	—	—	tropics, and subtropical areas
	Trichuriasis (whipworm)	—	—	world-wide
	Strongyloidiasis	dogs, cats, primates	Z	world-wide
	Trichinosis	pigs, rats	Z	world-wide
	Dracontiasis (guinea worm)	dogs	—	Africa, India, Iran
	The filariases:			
	Malayan and	dogs, cats	Z	Asia
	Bancroftian,	—	—	Africa, Asia
	onchocerciasis	—	—	Africa, South America
	loiasis	—	—	Africa
CESTODES	*Tapeworm*	cattle, pigs	Z	world-wide
	Hydatidosis	dogs, cattle, sheep	Z	world-wide
TREMATODES	*Schistosomiasis* (blood fluke)	domestic and wild animals	—	Asia, Africa, South America
	Fasciolopsiasis (intestinal fluke)	domestic and wild animals	Z	Asia
	Fascioliasis (liver fluke)	domestic and wild animals	Z	world-wide
	Opisthorchiasis (Chinese liver fluke)	domestic and wild animals	Z	Asia, Eastern Europe
	Paragonimiasis (lung fluke)	carnivores, fish	Z	China, Japan

1.3 GEOGRAPHICAL DISTRIBUTION

Parasitic diseases have a worldwide distribution (Fig. 1.2); the bacterial and viral diseases are the more common invasive diseases of temperate climates, while parasitic diseases are both common and widespread in tropical and subtropical areas and constitute a major health and economic problem. The high